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CONTENTS OF PREVIOUS NUMBER

OCTOBER, 1933. NUMBER 4

Primary Carcinoma of the Lung, with Special Reference to Incidence, Early Diagnosis and Treatment. Allan J. Hruby, M.D., and Henry C. Sweany, M.D., Chicago.

Diffuse Ulceration of the Esophagus and Trachea Associated with Diabetes Mellitus: Absence of Arteriosclerosis. Porter P. Vinson, M.D., and Russell M. Wilder, M.D., Rochester, Minn.

Human Capillaries in Health and in Disease. Irving Sherwood Wright, M.D., and A. Wilbur Duryee, M.D., New York.

Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine: Comparison of Their Effects When Administered Orally with the Effect of Thyroxine Injected Intravenously in an Alkaline Solution. Willard O. Thompson, M.D.; Phebe K. Thompson, M.D., and Lois F. N. Dickie, B.M., Chicago.

Benign Familial Polycythemia. Anthony Spodaro, M.D., and Claude E. Forkner, M.D., Boston.

Temperature of the Gastro-Intestinal Tract: The Effect Thereon of Hot and Cold Foods and of Physical Therapeutic Agents. Joseph S. Hepburn, Ph.D.; Harry M. Eberhard, M.D.; Rowland Ricketts, M.D., and Charles L. W. Rieger, M.D., Philadelphia.

Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with the Help of a New and Accurate Technic. Frances R. Vanzant, M.D.; Walter C. Alvarez, M.D.; Joseph Berkson, M.D., and George B. Eusterman, M.D., Rochester, Minn.

Nitrogen and Sulphur Metabolism in Bright's Disease: IV. Retention of Urea in the Nephrosis Syndrome. G. P. Grabfield, M.D., Boston.

Urea Clearance Test in Pregnancy. A. Cantarow, M.D., and G. Ricchiuti, M.D., Philadelphia.

Book Reviews.

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Archives of Internal Medicine

VOLUME 52 NOVEMBER, 1933 NUMBER 5

PERIODICITY OF CARBOHYDRATE METABOLISM AND RHYTHMIC FUNCTIONING OF THE LIVER

THEIR SIGNIFICANCE IN THE TREATMENT OF DIABETES WITH INSULIN

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STOCKHOLM, SWEDEN

If a diabetic patient is kept on a constant diet somewhat above his carbohydrate tolerance, with other conditions of life, particularly exercise, also constant, the amount of sugar excreted nevertheless will vary from day to day. If frequent samples of urine are examined, the excretion of sugar will be found to vary somewhat, independently of the meals. Some meals are followed by an immediate glycosuria, while others are followed by a slight increase or none. Closer investigation reveals these variations as expressions of a regular daily periodicity. Often in diabetic patients there is a minimum excretion of sugar around noon, even with a constant diet.

In severe diabetes during starvation, Hatlehol [1] found a continuous decrease in the sugar content during the day and an increase during the night, often with the greatest excretion in the early morning hours.

When first encountered, these phenomena were puzzling and inexplicable. Now light has been thrown on them by Forsgren's [2] discovery of the rhythmic functioning of the liver. Since Claude Bernard, the liver has been regarded as the body's chief storehouse of carbohydrate. Its glycogen content has been thought to express the balance between the supply of, and demand for, carbohydrates in the body. Somewhat contrary to this simple view, Forsgren has recently shown that the liver is no such passive storer of glycogen, but a rhythmically functioning organ, alternately storing glycogen and secreting bile. Through microscopic examination Forsgren found that the substance precipitated by barium in the liver of the rabbit varies considerably in amount at different times of the day. The barium precipitate consists chiefly of bile acids, and its quantity is in inverse proportion to the amount

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1. Hatlehol: Acta med. Scandinav. (supp. 8), 1924, p. 1.

2. Forsgren: Klin. Wchnschr. **8**:1110, 1929; Acta med. Scandinav. **73**:60, 1930.

of carmine-staining glycogen in the liver cells. In determining the glycogen content in the rabbit's liver by Pflueger's method, Forsgren found that it ranged from 1 to 13 per cent in a normal state of nourishment and from 0.25 to 2.5 per cent in starvation. These variations in the barium precipitate on the one hand and glycogen on the other exhibited a pronounced twenty-four hour periodicity, with a maximum amount of glycogen in the small hours of the night and early morning and a minimum at noon, at which time the bile elements were at their maximum. This periodicity was partly independent of meal times, and Forsgren considered it as the expression of a functional rhythm, with alternating secretory processes of assimilation and dissimilation in the liver. Corresponding variations were found in white mice by Holmgren [3] and Ågren, Jorpes and Wilander.[4]

That the liver in man functions with a daily rhythm is indicated by some earlier investigations. Thus Pfaff and Balch [5] found in a

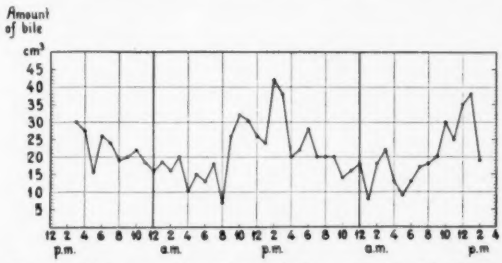

Chart 1.—Curve of bile secretion from Pfaff and Balch (J. Exper. Med. **2**:49, 1897).

woman of 38 with a postoperative blind biliary fistula that the maximum secretion of bile occurred periodically and could not be related to the meals. The secretion rose during the day and sank at night. The hourly secretion of bile was capricious and irregular. The greatest amount of bile was excreted at noon, irrespective of the hours for meals. A bile secretion curve of this type, published by Pfaff and Balch, is reproduced in chart 1.

From a comparison of Pfaff's and Balch's observations on secretion of bile, already mentioned, with Forsgren's discovery of the rhythmic functioning of the liver, it appears that in man also there is probably in the liver a maximum secretion of bile occurring simultaneously with a minimum glycogen content and a secretion minimum of bile together with a maximum glycogen content. According to the Pfaff and Balch

3. Holmgren: Ztschr. f. mikr.-anat. Forsch. **24**:632, 1931.
4. Ågren, Wilander and Jorpes: Biochem. J. **25**:777, 1931.
5. Pfaff and Balch: J. Exper. Med. **2**:49, 1897.

curve, one may thus expect a minimum of glycogen at noon and a maximum of glycogen after midnight.

The investigations of Mann and Magath [6] proved that the glycogen of the liver is the material used in the formation of the blood sugar.

Helly [7] found an abundance of glycogen in the livers of diabetic patients, and Paulesco [8] found the same in dogs with pancreatic diabetes after pancreatectomy. Moreover, it has been known since Claude Bernard and Pflueger that the liver can produce glycogen even in starvation. In diabetes, in which regulation of the blood sugar is disturbed, and in starvation, when no alimentary disturbances are manifest, Hatlehol also found a regular daily periodicity, viz., a decrease

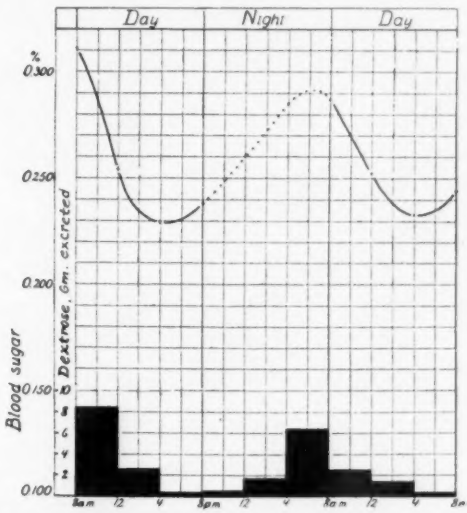

Chart 2.—**Blood sugar curve from Hatlehol** (Acta med. Scandinav. [supp. 8], 1924, p. 1).

of the blood sugar during the day and an increase at night, with a maximum excretion in the early morning hours. Chart 2 is a reproduction of one of Hatlehol's curves.

When food is taken, there is less regularity. The effects of absorbed nourishment, varying conditions of nutrition, excretion of sugar in the urine, etc., may be disturbing factors. However, sporadic observations have been made which suggest that even when nourishment is taken, the rhythm with which the liver functions may be manifest.

6. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, Arch. Int. Med. **30**:73 (July) 1922.

7. Helly: Ztschr. f. exper. Path. u. Therap. **15**:464, 1914.

8. Paulesco: Compt. rend. Soc. de biol. **83**:562, 1920.

K. Petrén [9] was the first to observe that in some diabetic patients the blood sugar curve has occasionally a tendency to sink toward the afternoon, irrespective of meals, and that blood sugar values may then be obtained which are lower than the starvation values of the morning. He also found that some meals are not followed by any increase in blood sugar, but he could give no adequate explanation for this. The rhythmic functioning of the liver gives a natural explanation of the phenomenon. It is only to be expected that the sugar curve will show reduced susceptibility to nourishment if a meal is absorbed during the assimilatory stage of liver function with a deposition of glycogen.

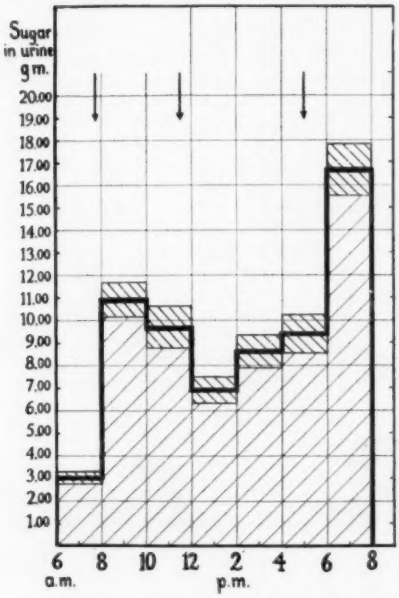

Chart 3 (case 1).—Urinary excretion of sugar.

Table 1 and chart 3 give the two hour sugar excretion of a subject who for twenty-three days was on a diet of 72 Gm. of protein and 160 Gm. of carbohydrate, the three daily meals being given at 7:45 and 11:30 a. m. and 5 p. m.

The time of the meals is indicated in the charts by arrows. The first and third meals were followed by a great and immediate increase in excretion, while after the second meal there was no such increase. This situation is particularly marked in patients kept on diets only slightly exceeding the limits of tolerance.

9. Petrén: Diabetes Studier, Copenhagen, Gyldendalske Boghandel, 1923.

In order to throw light on these questions, I made a systematic investigation of the effect of diet on the blood sugar curve. Tests were made on five different days. The food on the test days was always the same and consisted of twelve or twenty-four Albert biscuits,[9a] 96 Gm. of cheese, 96 Gm. of butter and 480 Gm. of milk. In addition, 100 Gm. of water was given every half hour. The composition of the meals was the same on each test day, but their number varied and the intervals between them ranged on the different test days from half an hour to four and a half hours. The capillary blood was tested by

TABLE 1.—*Excretion of Sugar in Case 1*

	Sugar in Urine, Gm. per 2 Hours						
	A. M.			P. M.			
1929	6-8	8-10	10-12	12-2	2-4	4-6	6-8
	a	a	a	a	a	a	a
October 7	1.4	7.8	12.7	5.2	3.2	3.7	17.6
8	3.1	13.9	20.0	5.9	5.1	5.8	13.3
9	2.2	6.4	15.2	6.2	3.8	7.5	12.5
10	2.6	10.6	9.9	6.3	7.1	11.5	13.4
11	2.0	5.0	6.8	6.4	6.3	20.4	15.6
14	4.8	8.9	8.6	6.9	4.4	5.7	7.8
15	2.3	9.0	5.4	5.9	7.2	4.9	33.1
16	3.7	11.7	19.7	11.5	16.4	6.7	7.0
17	2.5	8.8	9.1	3.3	7.4	10.3	19.4
18	2.6	8.1	8.8	4.6	11.8	9.5	13.2
21	5.5	14.5	11.3	10.7	7.9	12.3	21.9
22	3.6	18.1	7.4	7.9	9.0	9.2	25.9
23	4.3	16.0	12.6	8.6	16.2	12.8	17.9
24	3.0	8.0	10.3	6.7	10.8	4.8	10.5
25	2.0	5.9	12.6	5.6	9.9	10.8	16.3
28	3.1	13.7	4.4	6.8	10.8	14.4	21.7
29	2.3	15.4	6.3	1.8	9.8	10.8	22.5
30	0.7	10.0	10.0	7.5	11.5	12.3	28.2
November 5	3.7	10.9	8.6	9.6	11.2	12.4	8.8
8	5.4	12.3	3.0	2.3	9.3	11.2	15.4
13	0.9	10.3	7.8	12.2	6.9	4.2	16.3
14	3.2	8.9	7.8	9.7	7.5	10.5	13.7
15	3.9	17.3	3.7	6.8	3.8	3.4	11.4
M_a = ...	3.0±0.3	10.9±0.8	9.7±0.9	6.9±0.6	8.6±0.8	9.4±0.9	16.7±1.2

the Hagedorn method, specimens being taken at least every half hour from 8 a. m. to 8 p. m., with two or more starvation specimens between 7 and 8 a.m. Quantitative sugar and acetone tests were made on the urine, also every half hour.

The standard test series included the following daily tests: (*a*) twenty-four identical meals every half-hour from 8 a. m. to 7:30 p. m.; (*b*) eight identical meals, at 8, 9:30 and 11 a. m. and at 12:30, 2, 3:30, 5 and 6:30 p. m.; (*c*) four identical meals, at 8 and 11 a. m. and at 2 and 5 p. m.; (*d*) four identical meals, at 8 and 9:30 a. m. and

9a. The Albert biscuit is a standard biscuit used in Sweden, with the following constant composition per hundred grams: protein, 11 Gm.; fat, 4.6 Gm., and carbohydrate, 73.30 Gm., corresponding to 388 calories. Each biscuit has a weight of about 9 Gm.

at 12:30 and 3:30 p. m.; (*e*) four identical meals, at 8 a. m. and at 12:30, 3:30 and 6:30 p. m.

It then appeared that the blood sugar curves in the different daily tests varied. One meal might be followed by a marked, transient increase in blood sugar; another, by more prolonged hyperglycemia; a third might have comparatively little effect on the curve, etc. When the one and a half hour intervals were fixed at 8, 9:30, 11, etc., and the meals given at these hours immediately after the blood sugar determination (chart 4), irrespective of its shape otherwise, the difference curve for blood sugar values between 8 and 9:30 was an ascending one and between 9:30 and 11 a descending one; between 11 and 12:30 there was none, etc.

The daily periodicity is more distinctly apparent if the results of several test days are added, especially if the meal hours on the different

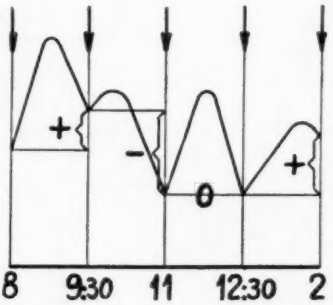

Chart 4.—Chart showing difference curve for values obtained at one and a half hour intervals.

test days are changed so that the more transient effects of alimentary irritation are neutralized.

In this investigation,[10] a total of one hundred and eighty-eight series of daily tests were made. The following is an example of these tests:

Case 2.—Hanna G., 62 years old, had cardio-arteriosclerosis and glycosuria.

Standard tests of types A, B, C, D and E were made on May 6, June 4, 14 and 21 and August 15. Table 2 and chart 5 give the values obtained for the excretion of sugar in the blood and urine.

The increase in the blood sugar content between 7 and 8 a. m. is noteworthy, since no food was given at that time. There was no external reason for the increase in the starvation value. This phenomenon is the same as that described by Hatlehol.

The difference curve is reproduced graphically in chart 6, which also includes data on the excretion of sugar in the urine and the time of the meals.

10. Möllerström, J.: Acta Soc. med. suecanae **56**:211, 1930.

TABLE 2.—*Results of Standard Tests in Case 2*

		May 6, 1929 Test A		June 4, 1929 Test C		June 14, 1929 Test D		June 21, 1929 Test E		Aug. 15, 1929 Test B	
		Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.
A. M.	7:00	119±7	0	149±2	0	164±1.5	0	154±1.5	0	134±0.5	0
	8:00	159±0	0	173±3.5	0	165±2.5	0	201±3.5	0	169±1.5	0
	8:15	163±10	0	167±2.5	0	—	0	192±1.5	0	180±1.5	0
	8:30	180—	0	186±1.5	0	175±1	0	208±2	0	186±1	0
	8:45	197±0	0	211±1	0	217±2	0	220±0	0	203±0	0
	9:00	197±3	0	227±2	0	224±0.5	0	234±1	0	215±2	0
	9:30	203—	0	229±2	0.23	223±1.5	0	227±0	0.24	223±0	0.07
	10:00	197—	0	220±0	0.20	233±1	0	206±0	0	226±0	0.06
	10:30	194±3	0	215±1	0	239±1	0.25	187±1	0	241±0	0.17
	11:00	190±1.5	0	186±1.5	0	222±1	0.24	166±2.5	0	233±1	0.35
	11:30	182±3.5	0	189±2	0	209±2	0.08	150±0	0	200±0	0.05
P. M.	12:00	205±1.5	0	188±1	0	205±0.5	0	123±4.5	0	206±1	0.08
	12:30	205±7.5	0	193±2	0	174±0	0	120±0	0	210±5	0
	1:00	194±3	0	197±2	0	183±0.5	0	151±1	0	179±0	0
	1:30	196±1.5	0	196±1	0	193±1.5	0	169±1	0	192±0	0
	2:00	188±3	0	178±0	0	194±0	0	180±1	0	194±2	0
	2:30	166±4	0	172±1	0	178±2	0	177±2	0	174±0	0
	3:00	193±9.5	0	176±0	0	171±0	0	167±3	0	200±3.5	0
	3:30	198±1	0.05	180±0	0	163±2.5	0	157±2.5	0	205±0	0
	4:00	192±2	0.05	175±1.5	0	184±3.5	0	173±0.5	0	191±1	0
	4:30	176±1	0.10	172±1	0	182±0	0	206—	0	199±1	0
	5:00	218±3	0.10	170±1	0	187±0	0	204±0	0	205±4	0
	5:30	220±4	0.10	169±0	0	187±2	0	196±1	0	203±2	0
	6:00	206±3	0.8	181±1	0	187±0	0	183±1.5	0	211±2	0
	6:30	239±2.5	0.10	216—	0	193±0	0	159±3	0	197±3	0
	7:00	236±1	0.20	222±2	0	183±1	0	171±0	0	190±1	0
	7:30	230±2	0.17	213±0	0.08	184±1.5	0	187±0	0	203±1	0
	8:00	223±1.5	0.20	193±2.5	0	166±0	0	198±2	0	183±1	0

From the primary observations the results given in table 3 were derived.

TABLE 3.—*Additional Data in Case 2*

		Blood Sugar Differences, Mg. per 100 Cc.															
		Starv. Value 7-8		8-9:30 A. M.		9:30-11 A. M.		11-12:30 A. M.		12:30-2 P. M.		2-3:30 P. M.		3:30-5 P. M.		5-6:30 P. M.		6:30-8 P. M.	
Test	Date	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
A.	5/ 6/29	40	..	44	..	..	13	15	..	..	17	10	..	20	..	21	..	..	16
C.	6/ 4/29	24	..	56	..	..	43	7	..	..	15	2	..	..	10	46	..	..	23
D.	6/14/29	1	..	58	..	..	1	..	48	20	..	..	31	24	..	6	..	..	27
E.	6/21/29	47	..	26	..	..	61	..	46	60	..	..	23	47	..	..	45	39	..
B.	8/15/29	35	..	53	..	11	..	..	23	..	16	11	..	0	..	..	8	..	14
		+147																	
		Σ		+237		−107		−95		+32		−31		+81		+20		−41	

		Sugar in Urine, Gm. per 1½ Hours							
Test	Date	8-9:30	9:30-11	11-12:30	12:30-2	2-3:30	3:30-5	5-6:30	6:30-8
A.	5/ 6/29	0	0	0	0	0.05	0.25	0.28	0.57
C.	6/ 4/29	0.23	0.20	0	0	0	0	0	0.08
D.	6/14/29	0	0.49	0.08	0	0	0	0	0
E.	6/21/29	0.24	0	0	0	0	0	0	0
B.	8/15/29	0.07	0.58	0.13	0	0	0	0	0
		Σ 0.54	1.27	0.21	0	0.05	0.25	0.28	0.65

Σ represents the value for the difference of curve.

In spite of the uniform meals, there was comparatively increased tolerance to nourishment between about 11 a. m. and 3 p. m. This is reflected in the excretion of sugar in the urine. When all the half-hour values are used, the same results are obtained, as chart 6 shows. This chart also includes a planimeter diagram.

For control, two new daily tests, *F* and *G* (chart 5), were made in which the same amount of food as in the other tests was given in a single meal. In test *F*, this meal was taken just before the first maximum of the difference curve, and in test *G*, seven hours later, corresponding to the minimum of the difference curve. In neither case had the subject taken any food since 5 p. m. the previous day. The interesting circumstance then transpired that in the former case the postalimentary hyperglycemia reached its maximum within one hour after the meal,

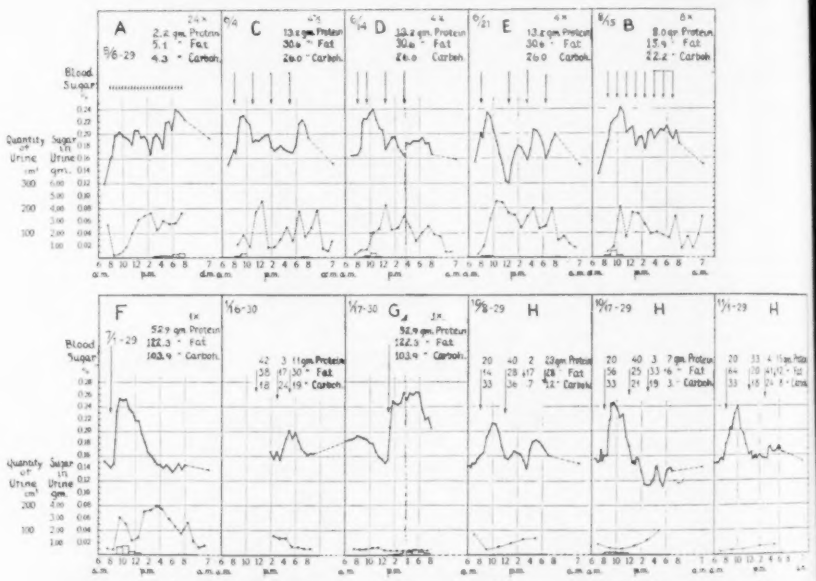

Chart 5 (case 2).—Curves for capillary blood sugar (solid line) and quantity of urine (dotted line). The crossed-barred areas indicate the amount of sugar in the urine.

and seven hours later it had disappeared. In the second case, on the other hand, the postalimentary hyperglycemia curve was of another type, not reaching its maximum until five hours after the meal, at a time when the difference curve presented its second maximum. The hyperglycemia had not yet disappeared after seven hours.

This dissimilarity in the course of the hyperglycemia curves may be explained by the consideration that digestion and absorption in the two tests took place at different phases of the functional rhythm of the liver. Obviously, a protracted effect is to be expected from the gradual digestion and absorption of so large an amount of food taken at one time.

In accord with the difference between the blood sugar curves, the sugar excretion in the urine also is of another type. Chart 7 shows in greater detail the sugar excretion in the urine at half-hour intervals for the two tests *F* and *G*. In test *F* there is early glycosuria, reaching its maximum after two hours and disappearing after five hours. The total amount of sugar passed with the urine in this case was 1.8 Gm. But if the meal is taken seven hours later, as was the case in test *G*, the glycosuria increases slowly, not reaching its maximum until four hours

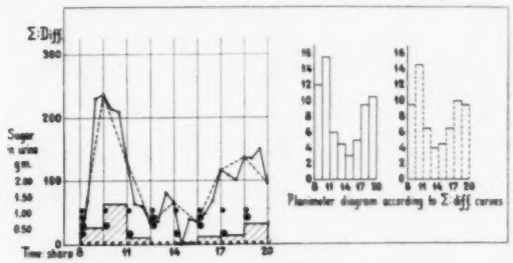

Chart 6 (case 2).—Difference curve with half-hour values (solid line) and hour and a half values (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

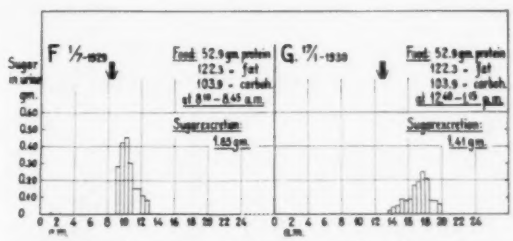

Chart 7 (case 2).—Urinary excretion of sugar.

later, at the time the difference curve for tests *A* to *E* shows its second maximum, and disappearing only after seven hours. The total amount of excreted sugar in this case was only 1.4 Gm. This verifies the supposition that the affinity of the liver for the absorbed nourishment differs at different stages of liver function; in the assimilatory stage with deposition of glycogen, the carbohydrate retention is greater than in the dissimilatory and secretory stage. The greatest affinity may reasonably be expected at the time when the dissimilatory stage changes into the assimilatory one, i. e., when the secretion of bile has passed its maximum. The bile secretion curve of Pfaff and Balch furnishes the key to the interpretation of this phenomenon.

The time of maximum secretion of bile, as shown in chart 1, is the same as that at which one sometimes finds the paradoxical decreases in blood sugar values already demonstrated by Petrén, *values which in spite of the intake of food are lower than starvation values.* Charts

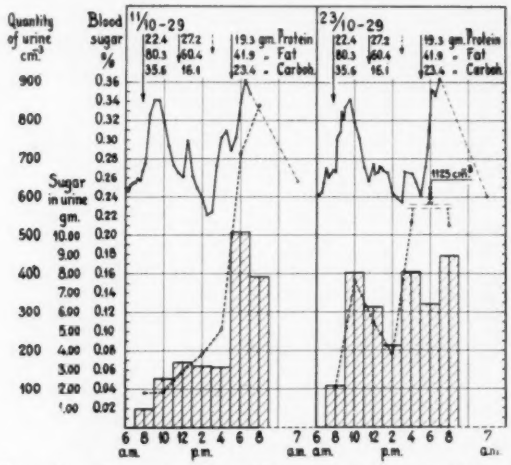

Chart 8 (case 1).—Curves for the capillary blood sugar (solid line) and quantity of urine (dotted line). The cross-barred areas indicate the amount of sugar in the urine.

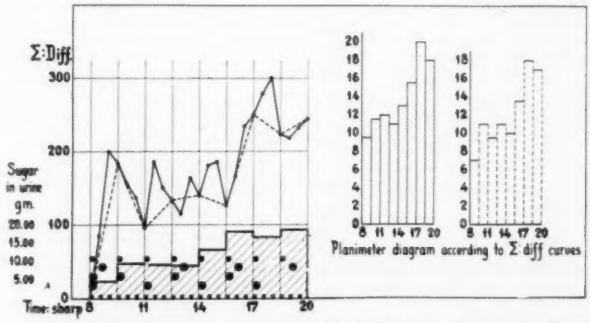

Chart 9 (case 1).—Difference curves with half-hour values (solid line) and hour and a half values (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

5 *E* and *H* and 8 give examples of this. Such a phenomenon cannot possibly be explained by differences in the emptying of the stomach, in digestion or in intestinal absorption, but it can very well be explained by reference to the periodicity of liver function.

The endogenous periodicity apparent in these difference curves varies in different subjects, as charts 9 and 10 show. In some cases the morning maximum of susceptibility to nourishment is greater, and the evening maximum less, while in others the reverse is true. In many cases, the morning and evening maxima are equal, and in these there is at noon a distinct minimum of sugar excreted in the urine. In cases of severe diabetes or an overburdened metabolism with a great excretion of sugar, this minimum susceptibility to nourishment is less pronounced.

The varying susceptibility to nourishment is not strictly bound to any special hour; it varies somewhat on different days, just as the secretion of bile varies (chart 1). The body's reaction to nourishment can also not be expected to remain constant at the same time of day

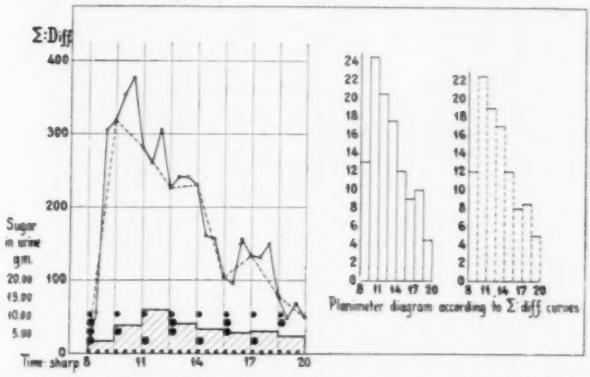

Chart 10 (case 13).—Difference curves with half-hour values (solid line) and hour and a half values (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

from one day to the next. Chart 11 shows how different the course of the blood sugar curve may be in the same subject under identical test conditions with uniform nourishment and with no change in the state of health.

In disturbances of the blood sugar regulation, when there is overburdening of the metabolism, interference phenomena will appear between the variable endogenous factors and the exogenous alimentary ones. This may cause considerable change in the course of the post-alimentary blood sugar curve, even when the external test conditions are constant. Endogenous factors may even dominate over the exogenous ones, a possibility which is of importance in a proper judgment of the problem of diabetes. Every food tolerance test in the practical and theoretical study of diabetes must therefore be judged

with caution so long as nothing is known of the endogenous periodicity and the capacity of the body to react to nourishment.

In addition to the daily rhythm of the function of the liver, there are, no doubt, periods of shorter and longer duration. Just as the bile secretion in the Pfaff and Balch curve shows minor rhythms in

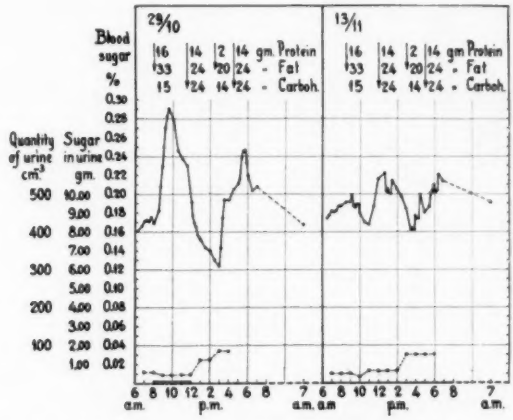

Chart 11 (case 30).—Curves for capillary blood sugar (solid line) and quantity of urine (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

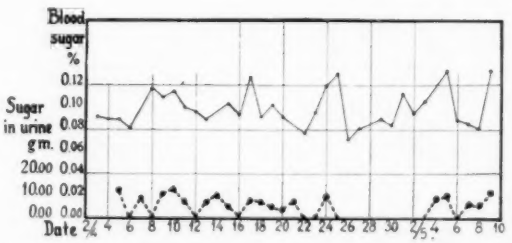

Chart 12 (case 14).—The upper curve indicates the blood sugar (starvation values); the lower curve, the sugar excreted in the urine with the patient on a constant diet.

daily periodicity, corresponding variations must be expected in the assimilatory and dissimilatory functions of the liver. To what this is due is still unknown. In the excretion of sugar of diabetic patients on a constant diet, a regular periodicity can also often be traced, spanning three, four or five days. Chart 12 shows a striking example of a long periodic excretion of sugar in a case of benign glycosuria.

For treatment with insulin, knowledge of the endogenous periodicity of the carbohydrate metabolism is of fundamental importance. Forsgren demonstrated in experiments on animals that susceptibility to insulin varies with the functional stages of the liver and its glycogen content. I found that in patients with severe diabetes treated with insulin in whom insulin shock had previously been observed, the latter regularly appeared at a time of day when, according to the standard tests already described, reduced susceptibility of nourishment could be ascertained.

Another example follows:

A diabetic patient, aged 71, excreted a mean amount of 67.9 Gm. of sugar daily on a diet of 34 Gm. of protein, 51 Gm. of fat and 81 Gm. of carbohydrate. On

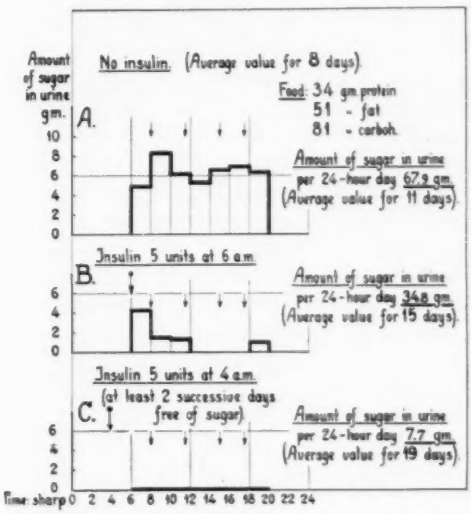
Amount of sugar in urine gm.
No insulin. (Average value for 8 days)
Food: 34 gm protein
51 - fat
81 - carboh.
A.
Amount of sugar in urine per 24-hour day 67.9 gm. (Average value for 11 days)
Insulin 5 units at 6 a.m.
B.
Amount of sugar in urine per 24-hour day 34.8 gm. (Average value for 15 days)
Insulin 5 units at 4 a.m.
(at least 2 successive days free of sugar)
C.
Amount of sugar in urine per 24-hour day 7.7 gm. (Average value for 19 days)
Time: sharp
0 2 4 6 8 10 12 14 16 18 20 22 24

Chart 13.—Urinary excretion of sugar in a patient with diabetes.

this diet, the patient was given 5 units of insulin at 6 a. m., after which the excretion of sugar diminished to a mean of 34.8 Gm. daily. But when the patient on the same diet was given 5 units of insulin at 4 a. m., the excretion of sugar fell to a mean of 7.7 Gm. daily, and, in addition, the urine was quite free from sugar eleven days out of nineteen.

This periodicity of excretion is shown by chart 13 *A*, which gives the mean amount of sugar excreted in the urine at intervals of two hours for eight days. Chart 13 *B* and *C* shows the sugar excretion on the same diet, but with 5 units of insulin given at 6 and 4 a. m., respectively.

This experiment shows that 5 units of insulin will not have the same effect at 6 a. m. as at 4 a. m., its effect at the latter hour being almost twice as great. Since the maximum sugar excretion of this patient took

place between 8 and 10 a. m., the most suitable time for giving insulin in this case was apparently four hours before the maximum excretion of sugar in the urine, irrespective of meals. Ingolf is about to publish a compilation of a large number of cases at the Maria Hospital, Stockholm, in which experience was gained concerning the administration of insulin in the early morning. Independently of my investigations, Tillgren and Ingolf found empirically in many cases that insulin had a more powerful effect when given in the early morning hours. Before the discovery of the endogenous periodicity of the carbohydrate metabolism, this was quite inexplicable. It is the endogenous periodicity of the carbohydrate metabolism, and not the meals, that should determine the dosage of insulin.

Without a doubt many factors cooperate, and the endogenous rhythm is an effect of interference with the cooperating factors, concerning which there is not yet sufficient knowledge. Forsgren's discovery of the rhythmic functioning of the liver indicates the direction in which a profounder study of the internal metabolism should be pursued.

Knowledge of the endogenous periodicity of the carbohydrate metabolism is probably of the greatest moment in the problem of diabetes, as much in diagnosis as in therapy. One may not take it for granted a priori that the reaction of the body is constant from one day to the next, or even from one hour to the next. Of late, the necessity has been emphasized of making daily blood sugar curves if one is to attain a rational insulin therapy. Seyderhelm and Oestreich stated that those cases of diabetes are more benign in which there is a distinct reduction of the noon value of the daily curve. In these, insulin is not considered necessary even when the starvation value of the blood sugar is comparatively high. If, on the other hand, the untreated diabetic patient shows a daily blood sugar curve with an ascending course, his case is regarded by Seyderhelm and Oestreich [11] as a severe one, requiring insulin treatment. The author's tests have a similar implication.

SUMMARY

In many cases of diabetes, there is a periodic variation in the effect of nourishment on the blood and urine sugar curves, irrespective of meals. At certain hours of the day, postalimentary hyperglycemia is milder and less prolonged, the sugar excretion in the urine also diminishing. There may be a tendency to spontaneous reduction of the blood sugar content, so that in spite of nourishment, blood sugar values are sometimes obtained which are less than the starvation values. The endogenous periodicity is different in different persons and may change slightly from one day to the next in the same person. This

11. Seyderhelm and Oestreich: Ztschr. f. klin. Med. **109**:35, 1928.

phenomenon is explained by Forsgren's discovery of the rhythmic functioning of the liver, with alternate glycogen production and bile secretion. In the assimilatory stage of the liver function with glycogen production, there is a tendency toward carbohydrate retention in the body, with reduction of the blood sugar content and of the excretion of sugar in the urine; in the dissimilatory or secretory stage the conditions are reversed. The endogenous periodicity of the carbohydrate metabolism is significant for the results of alimentary tolerance tests in diabetic patients, and appears to be of fundamental importance in the development of a rational insulin therapy. Insulin should be administered with due regard for the endogenous rhythm, and not for meal hours.

EPILEPSY AND CONVULSIONS IN DIABETES

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INCIDENCE

Extreme rarity of the coexistence of diabetes mellitus and epilepsy apparently has been accepted as a fact. According to Talbot (1930), "Study of the literature has so far failed to reveal a single report of the coincidence of idiopathic epilepsy and true diabetes mellitus." Trumper (1930) maintained that the theoretical incidence of epilepsy in persons with diabetes should be extremely small because of the ketosis and dehydration which are so constantly associated with diabetes and which are so antagonistic to epilepsy. Joslin (1928), writing about epilepsy, stated, "No clear cut case can be found among my 6,000 glycosurias of whom 5,086 are true diabetics." He did, however, mention several possible cases of epilepsy. Subsequent study of Joslin's diabetic patients furnishes the material for the present report.

Bolduan (1932) stated that 2.5 per cent of all deaths in New York City in 1931 were due to diabetes; and Weeks and co-workers (1923) said that "conservative authorities agree that fully 0.4 per cent of the total population" have epilepsy. A study of 19 patients suffering from both diseases is here reported.

Three phases of the subject will be discussed: convulsions dependent on diabetes, convulsions dependent on the diabetic therapy and epilepsy apparently merely coincident with diabetes.

CONVULSIONS DEPENDENT ON DIABETES

Convulsions as a manifestation of diabetes have been reported many times, particularly in the older literature. Kussmaul (1874) presented the history of a 16 year old diabetic patient with acidosis who was treated with alkali. Two days after treatment convulsions occurred and death ensued. Scheube's (1878) patient with jacksonian epilepsy recovered after the institution of alkaline therapy. Lepine (1888) reported the occurrence of convulsions in a person with severe diabetes. He attributed the symptom to intoxication with formic and oxybutyric acids, since at autopsy no cause was found other than much subarachnoid edema. Lossen (1905) added a case similar to the one reported by Kussmaul. Convulsions and death followed the use of alkali. Stauder's (1906) diabetic patient with convulsions who was relieved by alkali

From the Joslin Diabetic Unit, New England Deaconess Hospital.

was apparently not acidotic at the time of the seizures. Again, in 1911, Lepine reported a case of diabetic acidosis with convulsions following alkaline therapy. Chauffard and Rendu (1912) reported the case of a young diabetic and alcoholic patient with pulmonary tuberculosis who died following a series of convulsions and in whom at autopsy no renal or cerebral lesion was found. The treatment given was not stated. Labbé, as late as 1920, reported 4 cases of "acidotic epilepsy," in 3 of which alkaline therapy had been used. The treatment in the fourth case was not revealed. One of the patients lived for some time after recovery from the acidosis and suffered no more from convulsions, even in a subsequent and fatal attack of coma.

The experimental work in this field is meager. Gouget (1830) noted the occurrence of convulsions following the injection of acetone bodies into the brains of guinea-pigs. Von Jaksch (1886) produced convulsions in a rabbit placed under a bell jar containing acetone. Dufourt (1911) suggested that asphyxiation might have been the exciting factor, and the suggestion is borne out by the experience of Lennox and Cobb (1928). André and Baylac obtained no such result following the inhalation of acetone. Wilbur (1904) produced convulsions in rabbits by the intravenous administration of *beta*-oxybutyric acid.

Allen and Wishart (1923) studied the effect of the ingestion of various products of fat metabolism in animals. Convulsions were produced in two rabbits. One of these had been given diacetic acid by mouth, but the carbon dioxide-combining power of the blood rose from 38.6 volumes per cent fourteen and a half hours before death to 70 volumes per cent one hour before death. The convulsion occurred at the time of death. The other rabbit had been given butyric acid by mouth. There was a slight convulsion at death when the carbon dioxide-combining power was 33.8 volumes per cent, although this was 50 volumes per cent one and a half hours prior to death. A dog had a convulsion after the intravenous injection of butyric acid, but the carbon dioxide-combining power had been 89.6 volumes per cent only two and a third hours before the seizure and was 61.4 at the time of the convulsion, even after an infusion of saline. Certainly there is little about these experiences that suggests acidosis as the cause of the convulsions, and the authors attributed the convulsion occurring in the dog to alkalosis. Furthermore, Lennox, Nelson and Beetham (1929) found that rabbits fed fat or given injections of lactic acid or acetone were somewhat less susceptible to induced convulsions.

Explanations of this phenomenon have varied. Lepine (1888) attributed the convulsions to intoxication with formic and oxybutyric acids, although in 1909 he seemed to favor individual propensity rather than acetonemia. Dufourt (1911) reviewed the literature on the subject of acidotic epilepsy, and concluded that true diabetic coma is never

accompanied by epileptiform manifestations, and that the convulsions are usually due to uremia or to cerebral lesions or are merely coincidental. Labbé (1920) implied that Dufourt's statement is not entirely warranted, but admitted that it is strange that Naunyn in all his experience never observed convulsions in persons with acidotic diabetes. He concluded his article with the statement that diabetic epilepsy exists, and that it is a manifestation of acidosis and not of hyperglycemia.

Blum (1911) was among the first to assign to alkaline therapy a causative rôle in the production of convulsion in diabetic acidosis, although he admitted the rare existence of acidotic epilepsy. In 1913, in his description of the nervous complications in diabetic coma, he stated that intravenous injections of sodium bicarbonate gave rise to convulsions, whereas the administration of this drug by mouth had had no such effect in the cases he observed. He based his deductions not only on his clinical material but also on the experiments of Stadelmann (1885 and 1889), who produced convulsions in dogs by the injection of soda. However, reference to an article by Stadelmann in 1885 shows that this author used sodium carbonate rather than sodium bicarbonate, and that the symptoms produced in his dogs were so mild that he concluded it was a relatively harmless procedure. Again, in 1889, Stadelmann published the results of intravenous injections of a solution containing both of the aforementioned salts of sodium. Convulsions sometimes occurred in dogs so treated.

In recent years there has been a paucity of reports relating to this subject. Joslin, Root and White (1927) reported 63 cases of severe diabetic acidosis in which alkaline therapy was not used. One of the patients had convulsions, but tetanoid contractions occurred the tenth day after coma, at which time the carbon dioxide-combining power of the plasma was 80 volumes per cent. Thirteen days following coma, she died after a series of convulsions, although the carbon dioxide-combining power of the plasma had dropped to 43 volumes per cent. Autopsy showed marked congestion and edema of the meninges and brain with numerous punctate hemorrhages, in addition to many psammoma bodies and cholesteatomas, but the pathologist stated that no anatomic cause for death was found. Without considering the real cause of the convulsions, it seems fair to say that the ketosis previously present did not produce them.

In 1932, Joslin and his associates reported 179 cases of diabetic coma in which alkaline therapy was not used. Among these is included the case previously described. In addition, another case is described in which convulsions occurred. This case, 9783, was that of a man of 35 years who had had diabetes for three years but had been healthy in every other way. He entered the hospital thirty hours after the onset of symptoms of acidosis. He was drowsy and hyperpneic, but conscious. The carbon dioxide-combining power of the plasma was 4

volumes per cent. The response to treatment during the first six hours was satisfactory, but then the patient became weaker, had convulsions, was cyanotic, and died an hour later after further convulsions and increasing cyanosis. Just prior to death the carbon dioxide-combining power of the plasma was 23 volumes per cent, and the blood sugar, 0.44 per cent. The nonprotein nitrogen on admission was 39 mg. Autopsy was not permitted. Here one sees no definite cause for the convulsions. There was considerable cyanosis, which seemed to follow rather than to precede the convulsions, which appeared to be just a terminal phenomenon. If this case is one of acidotic epilepsy, at any rate it is the only one among 179 cases of diabetic coma. Since the publication of that series of cases, 36 more cases of diabetic coma have been observed in this clinic and in not one of them have there been convulsions.

Of all the published reports of acidotic epilepsy which I have read, none seems conclusive. Often pertinent facts are not given, and in some instances there are causes which seem more likely than the diabetic acidosis. Thus, it seems fair to say that acidotic epilepsy, if it exists, must be rare; and the fact that it was seen formerly when patients were treated with alkali and that it was not observed (with the possible exception of case 9783) in this clinic in a series of 215 patients with diabetic coma treated without alkali implies that Blum (1911) was right in attributing it to the alkaline therapy.

CONVULSIONS DEPENDENT ON THE DIABETIC THERAPY

The second phase of the subject of diabetes and epilepsy is closely related to the foregoing one, as may be judged from conclusions reached. One may assume that the alkalosis sometimes occurring after diabetic coma treated with or without alkali may give rise to convulsions in certain persons. It is well known that alkalosis may cause tetany (Collip, 1926, and Lennox and Cobb, 1928). Tileston (1917) stated that sodium bicarbonate administered intravenously caused tetany. Harrop (1919) reported the occurrence of tetany following the intravenous infusion of sodium bicarbonate in a case of anuria due to mercuric poisoning. I have already mentioned Stadelmann's experiments (1885 and 1889) in producing convulsions by the injection of alkali and also Blum's observations (1911 and 1913). Claude and Rafflin (1928) found slight alkalinity preceding epileptic seizures. Lennox and Cobb (1928) described cases in which there were increased epileptic attacks following a sudden swing from acidosis to alkalosis, although one patient had no increase in seizures following the slight alkalosis produced by feeding large amounts of alkali. Hence they concluded that "any sudden upsetting of the acid-base balance toward the alkaline side" may give rise to an increased number of epileptic attacks. This may well account for the convulsions formerly observed in diabetic

acidosis treated with alkali and is added reason for caution in the use of alkali in such cases, as has been pointed out by Joslin (1928).

But a more important phase of the subject nowadays is the use of insulin in the treatment of diabetes. The relationship between hypoglycemia and convulsive seizures is gradually attaining greater prominence in the literature. Behrendt and Hopmann (1924) and Waltner (1925) demonstrated that hypoglycemia is associated with an increased irritability of muscle or nerve tissue to galvanic stimuli. Wladyczko (1925) stated that there are epileptic persons whose attacks are provoked by hypoglycemia. Howland and co-workers (1929) and Carr and co-workers (1931) reported convulsions brought about by hypoglycemia resulting from a tumor of the pancreas. Removal of the tumor resulted in a cure. Convulsions due to injected insulin have often been reported (Joslin, 1928, and Woodyatt, 1922).

Any patient treated with insulin must be watched for hypoglycemic reactions, no matter how small the dose of insulin or how infrequently it is given. In case 8990 there was a mild hypoglycemic reaction fifteen and three-quarter hours after an injection of 6 units of insulin in spite of three intervening meals. Occasionally convulsive seizures represent a manifestation merely of hypoglycemia. Sometimes the cause of the convulsion is obviously hypoglycemia, either spontaneous, as in the case reported by Carr and co-workers (1931), or induced by injected insulin; but at times it is difficult to prove that hypoglycemia is the cause and the only cause. A few of our epileptic patients were at first thought to have had convulsions only as a result of hypoglycemia, but they had subsequent attacks without hypoglycemia, and this coupled with the later course of the condition indicated that they had true epilepsy.

The mechanism of the production of these convulsions is not well understood. Probably it could best be included under the explosive theory, as explained by Lennox and Cobb (1928, p. 129). Olmstead and Taylor (1924) found evidence suggesting that deficiency of oxygen might be related to the convulsions. MacLeod (1926) gave a good discussion of the mechanism of both the therapeutic and the toxic action of insulin. In 1928, he maintained that the upset in the neuromuscular mechanism must be caused, not so much by hypoglycemia per se, as "by some agent the development of which is normally prevented by the presence of a certain percentage of glucose." Furthermore, this convulsive phenomenon must occur through the intermediary action of the nervous system rather than by local change in the muscles, since section of the nerve supply to a group of muscles will prevent convulsions of these muscles even when convulsions occur in other groups of muscles.

Why some persons with hypoglycemia have convulsions and others do not is unknown. Possibly there is some epileptic tendency in the

former, which excessive stress may make manifest. It is interesting to note that 5 (cases 3019, 7089, 8042, 8217 and 10270) and possibly 6 (case 5562) of our epileptic patients were at first thought to have had convulsions due merely to a reaction from insulin. Twenty-five patients (cases 2476, 2528, 2633, 2979, 3778, 4022, 4242, 4650, 4715, 5181, 5615, 5830, 7145, 7191, 7592, 8213, 8217, 8316, 8657, 9077, 9382, 9736, 9782, 10442 and 11140) with convulsions apparently hypoglycemic have so far shown no other evidence of epilepsy. The patient in case 5615 had positive bilateral Babinski reflexes, but no cerebral lesion was found at autopsy; Anderson (1931) called attention to this finding in hypoglycemia and to its absence in diabetic coma. Subsequent observation of these cases will be of interest. The aforementioned 6 patients were children, and children are more subject to epilepsy and to hypoglycemic convulsions brought about by injections of insulin than are adults. It is generally conceded that anginal attacks (Hétenyi, 1927, and Root and Graybiel, 1931) or even coronary thrombosis (Blotner, 1930, and Parsonnet and Hyman, 1931) may be induced by an overdose of insulin, and Wohlwill (1928) reported cerebral lesions attributed to hypoglycemia. Drabkin and Shilkret (1927) noted intravascular clotting of blood in a dehydrated dog following the injection of insulin. Lawrence and Hollins (1928) reported 2 cases of hematuria attributed to insulin therapy. Combine these statements with Olkon's (1930) belief that "genuine epilepsy" is dependent on capillary hemorrhages occurring at birth, and one finds that there is some evidence favoring the supposition that hypoglycemia may occasionally be the cause of cerebral lesions which may give rise to epilepsy. Nevertheless, most of these clinical observations involved patients with a known potentiality for such vascular damage. However, the patient in case 3729, a young woman with no obvious arteriosclerosis, suffered for several days from what was believed to be monoplegia due to insulin, which began abruptly with unconsciousness and frothing at the mouth. Again, Joslin (1928) reported paralysis of a few days' duration caused by hypoglycemia thought to be due to insulin in a boy (case 2856) of 14 years.

In our cases of convulsions due to insulin we have noted no dehydration that might, according to Andrews and Schlegel (1927), have exaggerated the effect of insulin. Nor have we ever seen hypoglycemia cause convulsions in persons with diabetic coma, the condition causing the greatest dehydration in diabetic patients; and this is compatible with the assertion of Drabkin and Shilkret (1927) that the dose of insulin sufficient to cause hypoglycemic convulsions in normal animals caused no convulsions in dehydrated animals. Hypoglycemia seldom manifests itself clinically in cases of diabetic coma with or without unconsciousness. The absence of convulsions in persons with diabetic coma in whom hypoglycemia has been induced by treatment with insulin pos-

sibly may be explained partly by the presence of large amounts of fat and acetone (Lennox, Nelson and Beetham, 1929).

Convulsions in a diabetic patient should always be the signal for a determination of the blood sugar, since convulsions in diabetic patients are often due solely to hypoglycemia and are relieved promptly by the administration of an adequate amount of dextrose or other proper carbohydrate. The mere coincidence of convulsions and hypoglycemia should not preclude the diagnosis of epilepsy. Further observation and determinations of blood sugar during the seizures are necessary.

EPILEPSY APPARENTLY MERELY COINCIDENT WITH DIABETES

In the literature there is little concerning the coincidence of diabetes and idiopathic epilepsy except references to its rarity. The difference in the age incidence of diabetes and epilepsy discloses at least one reason for this rarity. Joslin (1928) stated that 66.6 per cent of his patients with diabetes had the onset of their disease after the age of 40 years, whereas Talbot (1930) compiled a table which shows that only 2.7 per cent of epileptic persons acquire epilepsy after the age of 40 years. The foregoing facts show the fallacy of Trumper's (1930) argument that "theoretically the incidence of epilepsy in diabetics should be extremely rare since ketosis and dehydration which are prominent features of diabetes constitute a mechanism which is in direct antagonism to the underlying features of epilepsy." The manifestations of epilepsy would have become apparent before the onset of diabetes in most persons suffering from the latter disease. Furthermore, control of the diabetes usually abolishes both ketosis and dehydration, especially during the present period when diabetic patients are given a fairly liberal allowance of carbohydrates.

Cases of diabetes associated with epilepsy have been reported. Lennox, O'Connor and Bellinger (1927) reported a case of epilepsy occurring with severe diabetes; and Allan (1932) reported 2 instances of epilepsy in a series of 840 diabetic persons. Joslin (1928) mentioned 2 of Dr. Geyelin's cases, and Talbot (1930) cited 2 cases seen by Lennox. Riesman and Fitz-Hugh (1927) reported 3 cases of diabetes associated with convulsions, and Labbé (1920) implied that there are diabetic persons with epilepsy.

Determinations of the blood sugar of epileptic subjects have been made often.[1] Usually the authors state that the values were normal.

1. See Lennox and Cobb (1928); Weston (1916); Heidema (1919); Schwab (1922); Kooy (1919); Olmsted and Gay (1922); Weeks and co-workers (1923); Holmström (1924); Nielson (1925); Drury and Farren-Ridge (1925); Lennox, O'Connor and Bellinger (1927); Lennox and Bellinger (1927); Osnato and co-workers (1927); Munch-Petersen (1928); Felsen (1930); MacKay and Barbash (1930).

but there is no widely accepted standard for normal. Joslin (1928) accepted as normal a blood sugar level below 0.14 per cent during fasting or below 0.17 per cent at any other time. According to this rigorous standard, there are among the epileptic persons for whom blood sugar determinations have been made many who might be classified as having diabetes. The series of 140 epileptic persons reported by Lennox and Bellinger (1927) contains 49 in whom at least one blood sugar determination was above 164 mg., although 21 of the 49 showed no glycosuria.

Among 9,503 patients with true diabetes seen by Dr. Joslin, there are now 19 with almost undoubted epilepsy, 6 of whom have subnormal mentality, and 3 who are classified tentatively as having epilepsy.[2] If one considers all 22 persons as having epilepsy the incidence of epilepsy among our diabetic patients is 2.3 per thousand. Using tables 25 and 50 (Joslin, 1928) and table 2 (Talbot, 1930) and an accepted incidence of epilepsy of 0.4 per cent among the general population (Weeks and co-workers, 1923) one computes a theoretical incidence of about 1.7 cases of epilepsy among 1,000 diabetic persons of all ages. If the figures of Partridge (1928) are used, the incidence is slightly less. Similarly, the incidence of epilepsy among diabetic persons with the onset of their disease before the age of 15 years is found to be 8.4 per thousand. Actually, we have 9 cases of epilepsy among 839 diabetic patients with the onset of the diabetes before the age of 15 years, thus giving an incidence of 10.7 per thousand among the children. This includes case 5562, which White (1932) attributed to hypoglycemia from insulin; but additional data and further consideration of the case persuade me that the attacks were probably epileptic and not hypoglycemic. However, the child was subject to reactions from insulin and the first epileptic attack may have been due to a hypoglycemia that gave rise to cerebral damage and thus caused the epilepsy, although there is no positive evidence that such damage occurs.

The differential diagnosis of epilepsy in the diabetic person is not always easy. A patient treated with insulin may be having a convulsion due merely to hypoglycemia. A diabetic patient with arteriosclerosis may be suffering from cerebral vascular lesions. Subsequent observation of the case is essential. If insulin has been injected, it is necessary

2. There is among our diabetic patients one (case 11252) with epilepsy which is attributed to a tumor of the brain by reason of headache, vomiting and papilledema. She has just been transferred to the neurosurgical service at the Boston City Hospital. This case is not included in the present series. Nor are two other cases, case 5367, which is one of definite epilepsy with glycosuria but without proved diabetes, and case 2364. The latter is that of a young man of 22 years, who had been subject to nocturnal convulsions, presumably of hypoglycemic origin; on one occasion he had a convulsion at 5:45 a. m., eleven and three-quarter hours after his previous dose of insulin, a time at which he usually excreted much sugar.

to have the blood sugar determined during each attack and preferably at its onset because, as Kersten (1921) and Rowntree (1926) have stated, the convulsion may give rise to an increase in the blood sugar.

In the cases occurring in children confusion in the diagnosis has occurred chiefly in differentiating between hypoglycemic convulsions and epilepsy. In elderly persons with diabetes one should distinguish between attacks of cerebral vascular disease, hypoglycemic convulsions and epilepsy. Careful and prolonged study of the patient usually clarifies the diagnosis. At any rate, it seems wise in such patients to change the dosage of insulin so that hypoglycemia does not occur, even though slight glycosuria results, and this is usually easily managed. After correction of the dosage of insulin, recurrent attacks of convulsions without subsequent aphasia, mental derangement or muscular paresis and without other obvious cause may well be classified as epilepsy.

The cases about to be presented here have been classified by Joslin first as cases of diabetes and second as cases of epileptic attacks without obvious cause. It is true the patients in cases 1745, 4273 and 5336 were arteriosclerotic, and their seizures, though of the usual epileptic type of both grand and petit mal, may have been dependent on vascular damage in the brain. Case 1745 is interesting in that the local doctor had observed rigidity of the left arm in the attacks, but following a shock which caused paralysis of the left side, no further seizures of any type occurred, even after recovery from the shock. Three years later, diabetes developed. Five years after the first shock the patient had a second on the same side and yet survived this for six years.

Three cases (5313, 7417 and 5562) are classified as doubtful cases of epilepsy: The patient in case 5313 for years had had attacks of stupor, clonic and tonic contractions, and nausea and vomiting. A member of the staff of the Boston Psychopathic Hospital saw her and was unable to say definitely whether the attacks were due to epilepsy or to hysteria. Subsequent to thyroidectomy no attacks occurred for two and a half years, but since then they have reappeared. The patient in case 7417, a woman, aged 38, had had sudden attacks of fainting without any recognizable cause. During one attack she had a convulsion. She had moderately severe diabetes and was taking insulin, but there was no definite evidence either for or against hypoglycemia from the insulin as a cause of the attacks. She had one brother who was a deaf-mute. The third doubtful case of epilepsy has been described. In the other cases there was no reason to doubt the diagnosis of epilepsy.

Diabetes developed in the patient in case 3019 in the nineteenth month of life. At the age of 28 months he began having convulsions, which were at first thought to be due to hypoglycemia. At the age of 3½ years he had an exanthematous infection, presumably measles,

with encephalitis as a sequel. At any rate, after this infection the seizures increased in frequency, and subsequently extreme mental deterioration occurred. Diabetes developed in the patient in case 8042 at the age of 2 years. At 3 years and 8 months, she was brought to the Children's Hospital unconscious and in convulsions. Previously well save for the diabetes, she had awakened laughing in the night and then had had a convulsion. Thereupon the mother gave her 8 units of insulin, although the usual daily dose of 5-0-5 units had been given the previous day. Another convulsion occurred after this. Twelve hours later at the hospital the blood sugar was 0.15 per cent, and the urine was free from sugar. Examination showed definite signs of meningeal disease or disease of the upper motor neurons. Slight intermittent fever followed for seven weeks, with temporary blindness which was attributed by the ophthalmologist to hypoglycemia, and by the pediatricians, to a possible toxic encephalitis. Subsequent to recovery from the infection, the patient had many epileptic attacks and underwent mental deterioration before her death in diabetic coma at the age of 5 years.

As for the diagnosis of the diabetes, there are 2 cases on which doubt might be cast. In case 7999, that of a girl of 13 years without evidence of nephritis, hypertension or any other disease except epilepsy and obesity, there was a trace of glycosuria and the blood sugar was 0.19 per cent. On an unrestricted diet, the patient subsequently had no glycosuria or elevation of the blood sugar. In case 5730, that of a boy of 17 years, there was a trace of glycosuria and the blood sugar was 0.18 per cent. Again there was no disease present except epilepsy. The other patients had definite diabetes, and in 9 the condition was severe. Nineteen of the 22 patients were at one time taking insulin.

In 8 cases the diabetes antedated the epilepsy. The reverse was true in 12 cases, and in 2 cases the onsets of the two diseases were simultaneous. In only 2 cases did the epilepsy cease before the onset of the diabetes, three years before in case 1745, and one year before in case 10353. In no case was it apparent that the diabetes or its treatment gave any relief from the epilepsy. Block (1928-1929) noted that epilepsy ceases after the development of tabes dorsalis. An analogous neurologic condition is rarely caused by diabetes, but so far we have observed the occurrence of it in none of our diabetic patients with epilepsy. Occasionally hypoglycemia from insulin seemed to give rise to a greater number of epileptic seizures as in cases 3019, 5562 and 7089.

The age at the onset of each disease in each patient is given in the accompanying table. In 9 cases the diabetes began before the age of 15 years, and in 7 cases, after the forty-fifth year of life. In 10 cases the epilepsy began before the age of 15 years, and in only 4 cases, after the forty-fifth year.

Concerning the etiology of the epilepsy in these cases, I have listed the doubtful cases and the alternative diagnoses. Two of the children had had intestinal parasites, and 3 of them had infected tonsils. Two patients (cases 5513 and 8514) had thyroid disease; in the former instance the disease was nontoxic and in the latter, toxic. One patient (case 5730) had a skull of the oxycephalic type, and there was some question of hypopituitarism in another patient (case 8622). Vascular disease was present in cases 1745, 4273, 5313, 5336 and 7196. There was a history of injury to the head at the onset of the epilepsy in cases 10645 and 11009. In contrast with the implications in papers by Rome (1911), Spielmeyer (1930), Olkon (1930) and Fincher and Dowman (1931), in most of the cases no definite evidence of organic disease of the brain was found. Neither was heredity apparently important, although careful histories for an epileptic heredity were not taken. The patient in case 6313 had one sister with a tumor of the brain. The patient in case 7417 had a brother who was a deaf-mute. There was a family history of defective mentality, feeblemindedness or epilepsy in cases 5730, 7089 and 10783. Incidentally, diabetic heredity was present in 9 cases, in none of which there was a family history of mental derangement or epilepsy.

The epilepsy in 3 cases has shown some relationship to the menses. The patient in case 7196 had grand mal prior to the menopause, but only petit mal since. In case 11009 the patient had more than twice as many seizures before the menopause as she had subsequently. Pregnancy increased the number of her seizures but only until parturition. The epilepsy in case 10353 began at puberty and ceased seven years before the menopause. The attacks always came just a few days before the menses, although remissions of six months' duration occasionally occurred. Lennox and Cobb (1928) referred to the "well-known fact that many female patients frequently have seizures near the time of menstrual periods," and they listed the appropriate references. They explained this relationship on the basis of "the increased nervous irritability which many women exhibit at that time." Partridge (1928) and Healey (1928) implied belief in such a relationship. Souques (1931) divided such cases into two types: in the first, epilepsy is associated with normal menses, pregnancy and the period following the menopause, and in the second the seizures occur with abnormal menstruation and disappear with the establishment of normal menses. Okey and Robb's (1925) finding of a decreased tolerance to sugar just before and just after the menses and an absence of any consistent cyclic variation in the blood sugar level during fasting in women tends to exclude hypoglycemia as a cause for frequent epileptic seizures at such times. Okey and Robb did find, however, that the ingestion of dex-

trose led to greater secondary hypoglycemia during menstruation than at any other time.

In the table are listed various observations which may be of interest in comparison with similar data on epileptic persons without diabetes.

Nielson (1925) found an average basal metabolic rate of minus 10 per cent in 18 epileptic persons. Lennox and Wright (1928), in a study of 130 such patients, obtained an average value of minus 3 per cent. Lennox and Cobb (1928) stated that the majority of adults with convulsions have either a normal or a reduced rate of oxygen consumption. Joslin (1928) pointed out that the metabolism in diabetes varies not so much from intrinsic as from extrinsic causes of which the diet is the chief one, and he stated that the metabolism in diabetes varies but little from normal. White (1932), in a study of 86 diabetic children and 17 adolescents with diabetes, found the average basal metabolic rate to be plus 11 per cent (in girls, but plus 12 per cent in boys) and minus 2 per cent, respectively. In 9 of our diabetic patients with epilepsy the average metabolism was plus 4 per cent.

In spite of much study of the blood cholesterol, little definite knowledge has been acquired. Pezzali (1923) found a decrease in the blood cholesterol during epileptic fits, but a subsequent rise. Osnato and co-workers (1927) obtained an average blood cholesterol by the method of Myers and Wardell (normal, from 140 to 160 mg.) of 140 mg. in 22 epileptic patients on a diet consisting of 150 Gm. of carbohydrates, 120 Gm. of protein, and 150 Gm. of fat. They found no correlation between the seizures and the level of the cholesterol. Robinson, Brain and Kay (1927) observed a lower average level of cholesterol in epileptic patients than in normal persons, and a low or falling level of cholesterol prior to the seizures. Goodall (1929) also noted that the blood cholesterol was lower preceding the seizures than in the period between attacks. Gosden, Fox and Brain (1929) obtained low values for epileptic persons, especially within twenty-four hours of a seizure. Their lowest values were obtained in status epilepticus or serial epilepsy. This is in contrast to the emotional hypercholesteremia observed by Lyons (1931). These two papers thereby give evidence that the epileptic convulsions may not be associated with hyperactivity of the sympathetic nervous system to which Tracy (1926) attributed them, since in sympathectomized animals Lyons obtained no hypercholesteremia. The publications of Bloor (1931) and Rabinowitch (1931) make it obvious that a proper interpretation of cholesterol values cannot be made unless the diets of the subjects are taken into consideration. In agreement with this is Barborka's (1930) finding that the level of the cholesterol in his epileptic patients was low, and that a ketogenic diet caused an elevation of cholesterol. In the cases herein described, the cholesterol values are influenced not only by the diet but also by the diabetes or condition

Case	Age of Patient at Onset of Epilepsy	Age at Onset of Diabetes	Severity of Diabetes: Mild	Moderate	Severe	Weight in per Cent of Normal*	Basal Metabolic Rate	Plasma Bicarbonate, Mg.	Chlorides, Mg.	Calcium, Mg.	Phosphorus, Mg.	Cholesterol, Mg.	Diet After Onset of Epilepsy: Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Later Diet: Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Effect of Change in Diet
1745	53.0	65.0	+	..	..	+17	..	..	663	....	...	...	No restriction			...	..	..	
																Peterman diet			
3019	2.3	1.6	..	..	+	−17	−6 to +9	..	...	....	4.4	203	...	..	...	16	15	78	Later carbohydrate and no attacks for 23 days
4273	57.0	59.0	..	+	..	+25	..	49	507	....	...	...	88	57	128	131	65	89	No apparent effect
5313	38.0	38.0	..	..	+	+ 5	−1 to −2	..	...	....	...	...	78	60	117	100	66	94	No apparent effect
5336	62.0	67.0	+	..	..	−11	..	52	...	....	...	...	133 (?)	41	54	...	..	..	
5562	9.5	4.8	..	..	+	....	+5 to +17	52	...	10.4	...	...	84	57	93	45 to 96	..	..	No apparent effect
5730	16.0	17.0	Very mild	..	..	−10	..	..	...	....	...	...	...	..	...	...	..	..	
7089	10.0	2.0	..	..	+	+8½	+20 to +51	..	...	....	...	...	32 to 85	50 to 60	80 to 100	...	..	..	No apparent effect
7196	24.0	53.0	+ to +	..		+12	..	..	...	....	...	...	61	54	42	80 to 147	48	73	No apparent effect
7417	33.0	36.0	..	+	..	+ 2	..	50	...	....	...	...	110	77	135	124	64	93	No apparent effect
7999	10.0	13.0	+	..	..	....	−7	..	...	....	...	...	...	..	...	...	..	..	
8042	3.7	2.0	..	..	+	....	..	..	...	....	...	185	...	..	...	...	..	..	
8217	8.0	4.5	..	..	+	−3½	..	..	...	....	...	263	84	47	84	116	73	92	Also has phenobarbital; fewer attacks
8514	26.0	38.0	+ to +	..		+32	+65 to +18	..	...	....	...	...	120	68	120	122	67	119	
8622	Prior to diabetes mellitus	12.0	..	..	+	N	−9	..	...	....	...	108	75	51	86	102	62	115	
9010	37.0	59.0	..	+	..	−24	..	..	...	....	...	...	40	60	100	115	56	87	
10270	11.0	6.0	..	..	+	−12	+8	49	450	9.0	2.1-3.9	120-206	129	78	104	180	86	84	
10353	13.0	39.0	.	+	..	−20	..	..	...	....	...	...	Unrestricted			...	..	..	
10645	5.0	11.0	..	..	+	−10	..	47-54	467	11.3	5.1	216-182	Unrestricted			158	76	81	No apparent effect
10783	45.0	45.0	+	..	..	+18	−6	50	...	....	...	242	158	82	133	...	..	..	
10785	22.0 (?)	23.0	..	+	..	−19	..	..	...	....	...	...	Unrestricted			134	69	93	No apparent effect
11009	15.0	57.0	..	+	..	N	−5	52	485	11.7	3.6	298	Low carbohydrate to high carbohydrate						No apparent effect

* The weight is that at the onset of epilepsy, if known; otherwise the weight is that when the patient was first seen by us.

associated with it. Nevertheless it seems worth while to include them. The average value for the 8 cases studied is 207 mg. (normal, from 180 to 230 mg.).

Spinal puncture was done in 7 of our cases of epileptic diabetes. No evidence of a pathologic process was found, although the total protein was 19 mg. and 15 mg. in 2 of the cases. In 2 cases simultaneous venipuncture was done. In 1 the blood sugar was 0.32 per cent when the spinal fluid sugar was too low to be measured. At the time, the patient was under the influence of ethylene anesthesia. In the other case the blood sugar was 0.26 per cent when the spinal fluid sugar was 0.11 per cent. The ratio of spinal fluid sugar to blood sugar in these cases is considerably lower than that reported by Lennox and Allen (1930) and that by Wahl (1931). Patterson (1929) found spinal fluid sugar low in epileptic persons, but gave no figures.

In the light of recent publications concerning the treatment of epilepsy, it seems advisable to discuss briefly dehydration, ketosis and acidosis in diabetes and the factors influencing them. It is well known that persons with diabetes often become dehydrated, usually owing to lack of treatment. The patient in case 10785 entered the New England Deaconess Hospital with a glycosuria of 8.3 per cent. In the next four days his weight increased from 118½ to 125¼ pounds (53.7 to 56.8 Kg.), and the dryness of the skin and mouth disappeared. If the diabetes has advanced still further, ketosis occurs with the excretion of acetone bodies through the kidneys and the lungs. Sometimes even then there is no appreciable lowering of the carbon dioxide-combining power of the plasma (case 11020), although often there is. As the ketosis increases, the carbon dioxide-combining power decreases, until at times it descends as low as 1.1 volumes per cent (Olmstead, quoted by Joslin, 1928). Diabetic treatment combats and eventually overcomes these three conditions. The carbon dioxide-combining power rises, the ketosis disappears, and soon the patient appears healthy without signs of dehydration. As a matter of fact, I have seen no reports concerning the carbon dioxide-combining power of the plasma in properly treated diabetic persons during the insulin era. Of course, prior to insulin therapy, mild ketosis and acidosis existed for long periods in some diabetic persons, even in those given the best of treatment, and almost all the children died in coma in spite of treatment. However, this is no longer true.

Persons with epilepsy, on the other hand, seem to have no evidence of dehydration, ketosis or disturbance of the acid-base equilibrium of the body fluids during the interparoxysmal periods. Lennox and Cobb (1928) referred to "the polyuria which frequently succeeds a convulsion," but they apparently attribute it to the accumulation of acid substances produced by the muscular work of the convulsion. In our cases

we have noted no such polyuria and no change in the weight of the patients at such a time, possibly because we have made no special study of this phenomenon. Ketosis apparently has not been noted in epileptic persons under ordinary conditions, and, except in evident acidosis, was present in only 7 of our cases. This ceased with treatment. There are, however, many observations on the acid-base equilibrium in epilepsy. Lennox and Cobb, in 1928, summarized the literature up to that time, and concluded that the acid-base balance is essentially normal between seizures, although there may be an abnormal degree of variation from day to day. Lennox (1928) found the carbon dioxide-combining power of the plasma within normal limits in 88 of 100 epileptic persons and above 70 volumes per cent in 12. Claude and Rafflin (1928) found slight alkalinity preceding the attacks. Shera (1928) found no decrease and possibly some increase in the alkali reserve without regard to the attacks. We have made determinations of the carbon dioxide-combining power of the plasma in 8 of our patients without obvious diabetic acidosis. The values ranged from 47 to 54 volumes per cent, with an average of 50.6 volumes per cent. During diabetic acidosis the value in 1 case was 24 volumes per cent. Four other patients have at one time or another been definitely acidotic; 2 of them have been in coma.

TREATMENT

None of our epileptic patients have received any treatment for the epilepsy except the administration of sedatives. Phenobarbital was used in 10 cases with some benefit. Bromides apparently afforded relief in 2 cases. Thyroid extract was given in case 3019, as much for the patient's general condition as for any other reason. At first this seemed to decrease the epileptic attacks, but later the disease progressed markedly.

Since the papers of Guelpa and Marie (1910), Geyelin (1921) and Wilder (1921), there have been many publications [3] about fasting, ketogenic dietary regimens and dehydration in epilepsy. The observations of many workers [4] help to explain the benefit of these regimens so frequently noted in epilepsy. However, some studies [5] of the subject

3. Hoeffel and Moriarty (1924); Shaw and Moriarty (1924); Talbot, Metcalf and Moriarty (1927); Peterman (1927 and 1928); Lennox and Cobb (1928); Lennox (1928); Geyelin (1929); McQuarrie (1929); McQuarrie and Husted (1929); Higgins (1930); Talbot (1930); Helmholz and Keith (1930); Barborka (1930); Fay (1930); Doolittle (1931); Bridge and Iob (1931).

4. Weir, Larson and Rowntree (1922); Gamble, Ross and Tisdall (1923); Rowntree (1926); Lennox (1928); Lennox, Nelson and Beetham (1929); Gamble (1929); Bridge and Iob (1931); McQuarrie and Peeler (1931).

5. Peterman (1927); Nelson (1928); McQuarrie (1929); Higgins (1930); Barborka (1930); Guthrie (1930); Greer (1930); Regan (1931).

have attributed minor deleterious effects to these methods of treatment. On the other hand, Talbot (1930) found that the ketogenic diet caused no disturbance of normal growth and development, and Higgins (1930), Helmholz (1932) and Clark (1932) expressed the belief that such a diet helps to overcome infection.

One might suppose that diabetic persons with epilepsy would be especially favorable subjects for such regimens, because in former years fasting and ketogenic diets were the accepted mode of treatment for diabetes, and the disease itself would enhance the results obtained. Yet many of the large diabetic clinics have abandoned the diet low in carbohydrates and high in fats. Such a diet is obtained with some difficulty, is not generally so satisfying to the patients as one containing at least 100 Gm. of carbohydrate, and seems more prone to cause languor and lassitude. There is good evidence that it induces hypercholesteremia, and it is considered in this clinic to be a predisposing cause of the premature arteriosclerosis so often seen in diabetic persons.

We have not thought it wise to use a ketogenic diet. Reference has been made to the disadvantages of this treatment. Furthermore, it seems unsafe to keep a person acidotic who not infrequently becomes severely acidotic and who might die, as others have, from such an acidosis. To a dehydration regimen a similar objection may be made, though the risk is less. However, there may be cases which should be made exceptions on account of uncontrolled epilepsy. Uncontrolled severe diabetes very simply accomplishes the results of both treatments, and yet I dislike to recommend neglect of one serious disease because of another.

SUMMARY AND CONCLUSIONS

1. The literature on convulsions attributed to diabetes or to its treatment has been reviewed, and pertinent data have been collected from our diabetic patients and set forth. 2. The evidence so far tends to discredit the idea that diabetes per se causes convulsions, but it is equally evident that excessive administration of either alkali or insulin may give rise to such seizures. 3. The appropriate literature concerning idiopathic epilepsy in persons with diabetes has been analyzed and correlated, and observations on our 22 cases have been added. 4. The incidence of epilepsy in diabetic persons seems to be similar to the theoretical incidence in unselected people of corresponding age groups.

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TOXIC CIRRHOSIS CAUSED BY CINCHOPHEN

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Shortly after the introduction of cinchophen into the therapeutic armamentarium, patients revealing toxic effects were observed, and their cases were reported in the literature. In 1922, Schroeder [1] reported a series of cases, and urged caution in the use of the drug. In 1923, Worster-Drought [2] first reported the occurrence of jaundice as a toxic manifestation. The toxic symptoms are of various types: cutaneous, anaphylactoid, gastro-intestinal, cardiac, renal and hepatic. An extensive review of the question of the toxicity of cinchophen is being prepared by our colleague, Dr. Hench.[3] In this paper we are concerned only with cases in which there were hepatic manifestations. We have been able to find 98 cases reported in the literature, exclusive of those previously reported from the Mayo Clinic. The latter cases, together with others reported now for the first time, total 19, in 5 of which the results were fatal. This gives a total of 117 cases; in 61 the patients died, and in 45 necropsy was performed. This paper is a study of the clinical features of these cases so far as the data available are concerned, with particular reference to the cases from the clinic; we personally have cared for the majority of the latter patients.

Cinchophen (2 phenyl-quinoline, 4 carboxylic acid) was introduced by Nicolaier and Dohrn [4] in 1908 as an agent in the treatment of gout. Although its efficacy in the removal of tophi was not substantiated by clinical experience, its effect on purine metabolism was soon proved. The analgesic effect was also notable, and it soon was extensively used in place of salicylates for relief from pain caused by various rheumatic conditions. This was in part to escape the unpleasant effects

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From the Division of Medicine, the Mayo Clinic.

1. Schroeder, K.: Cases of Cinchophen Poisoning, Ugesk. f. læger **84**:1141 (Sept. 7) 1922.

2. Worster-Drought, Cecil: Atophan Poisoning, Brit. M. J. **1**:148 (Jan. 27) 1923.

3. Hench, P. S.: Derivatives of Cinchophen and Their Toxicity, Proc. Staff Meet., Mayo Clin. **7**:427 (July 20) 1932.

4. Nicolaier, Arthur, and Dohrn, Max: Ueber die Wirkung von Chinolincarbonsäuren und ihrer Derivate auf die Ausscheidung der Harnsäure, Deutsches Arch. f. klin. Med. **93**:331, 1908.

of salicylism. In 1923, Brugsch and Horsters [5] demonstrated the cholagogic effects of cinchophen on animals and on patients with biliary fistulas. An increase occurred in both the fluid and the total solid content of the bile. However, after large doses or after administration over a long period, both the fluid and the solid content fell below normal after the initial increase. Brugsch and Horsters interpreted this as being due to injury of the hepatic cells. Later, however, Brugsch [6] maintained the innocuous properties of the drug, and recommended its use in the treatment of subacute yellow atrophy of the liver. Other investigators similarly have demonstrated a cholagogic effect, and Traubman [6] stated that cinchophen is excreted in the bile. Thus it has been used in various forms; for example, as icterosan it has been used in the treatment of catarrhal jaundice and other hepatic conditions.[7]

In view of these facts, it was a logical step when Pribram [8] introduced biloptin (diiodo-cinchophen) in 1926 as a cholecystographic medium. Einhorn and Stewart and Einhorn, Stewart and Ryan [9] introduced it in America in 1927. Spurling and Hartman [10] reported on the effect of tolysin (neocinchophen) as an adjunct to iso-iodokon (phenyl-*tetra*-iodophenolphthalein sodium) in cholecystography. The administration of 15 grains (1 Gm.) of tolysin an hour before giving iso-iodokon apparently increased the rate of elimination of the dye. From further experiments Spurling and Hartman felt that possibly the phthalein compound produced some hepatic injury. However, on reviewing their tables one is impressed with the probability that the injury is due to the effects of the tolysin. In 1931, Lichtman [11] advocated the use of oxycinchophen as a determinant of hepatic function. If hepatic lesions are present, increased amounts of this compound are excreted in the urine.

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5. Brugsch, Theodor, and Horsters, Hans: Cholerese und Choleretica, ein Beitrag zur Physiologie der Galle, Ztschr. f. d. ges. exper. Med. **38**:367, 1923.

6. Quoted by Davis.[12]

7. (*a*) Dassen, Rodolfo: Sobre la acción hepatotóxica de los derivados de la fenilquinoleina, Semana méd. **36**:368 (Feb. 14) 1929. (*b*) Nathorf and Willert, quoted by Adler, A.: Therap. d. Gegenw. **67**:174 (April) 1926. (*c*) Weiss, Samuel: Acute Yellow Atrophy of the Liver: Acute Necrosis of the Liver, M. J. & Rec. **135**:316 (April 6) 1932.

8. Pribram, quoted by Einhorn, Stewart and Ryan.[9b]

9. (*a*) Einhorn, Max, and Stewart, W. H.: On Hepatography, M. J. & Rec. **126**:430 (Oct. 5) 1927. (*b*) Einhorn, Max; Stewart, W. H., and Ryan, E. J.: Experiences with Biloptin (Diiodoatophan) for Cholecystography by Oral or Duodenal Method, ibid. **125**:457 (April 6) 1927.

10. Spurling, R. G., and Hartman, E. E.: Serum-Colorimetry and Other Evidence of the Choleretic Action of Tolysin (Ethyl Ester of Paramethyl-Phenylcinchoninic Acid) in Man, J. Lab. & Clin. Med. **13**:854 (June) 1928.

11. Lichtman, S. S.: Cinchophen Oxidation Test of the Function of the Hepatic Cells, Arch. Int. Med. **48**:98 (July) 1931.

Cinchophen is marketed in many forms, and many derivatives have been prepared. The quinoline radical is the essential nucleus of all these preparations. Hench listed a large series of such forms in which cinchophen is available. Unfortunately, it has not always been given under medical supervision. Moreover, it has been used by physicians without adequate knowledge of its dangers. Recently a patient presented himself giving a history of painless jaundice for five weeks following the use of oxyliodide (cinchophen hydroiodide) for arthritis. His physician had urged exploration for cholecystitis. The laity has learned of its analgesic effects and has purchased at drug stores large amounts of it and of patent medicines the active principle of many of which is largely cinchophen.

Chief of the various preparations which contain cinchophen are atophan (cinchophen) and oxyliodide. Other preparations, some of which have been mentioned, are biloptin, icterosan, neocinchophen, atoquinol (allyl phenylcinchoninicester), atophanyl (cinchophen sodium, sodium salicylate and procaine hydrochloride), quinophan (cinchophen), farastan (mono-iodo-cinchophen), Harrell's, Van Ard's and Cass' preparations, Gorum cachets and Renton's hydrocine tablets. There are many preparations on the market following the use of which cases of toxic cirrhosis have not been reported, but as Hench has pointed out, since estimates as to the total quantity of each preparation consumed are not available, conclusions as to their relative toxicity cannot be drawn. Further, as pointed out later, all cases are not reported, and others are not recognized.

Various hypotheses have been advanced as to the cause of the toxic symptoms, namely: breaking free of the benzene nucleus or the formation of toxic nitrocompounds from the quinoline nucleus; an impure form of the drug; an increased suceptibility of the liver from injuries such as alcoholism, eclampsia, cholecystitis, cirrhosis, starvation and undernutrition; other lesions producing jaundice; chronic infections generally, and sensitization of the liver from the administration of foreign protein. It is fairly definitely demonstrated that certain persons have an idiosyncrasy to the drug. However, the recent statement of Davis [12] seems justified: "No explanation at present exists for the toxicity of cinchophen except hypothesis."

Experimental work also has failed to solve the problem of toxicity. Most investigators have failed to produce hepatic injury in animals by the use of cinchophen. We know of only one investigator (Biberfeld [13]) who has reported such experimental injury; he produced toxic

12. Davis, J. S., Jr.: The Relation of Neocinchophen to the Question of Cinchophen Toxicity, Am. J. M. Sc. **184**:555 (Oct.) 1932.

13. Biberfeld, J.: Zur Wirkungsweise des Atophans, Ztschr. f. exper. Path. u. Therap. **13**:301, 1913.

cirrhosis in a dog after the administration of 75 grains (5 Gm.) of cinchophen. The explanation may be that only some animals, just as only some human beings, are susceptible to the drug.

On account of these reported effects of cinchophen, various suggestions have been made as to the proper method of administration of the drug to avoid toxic results. Thus, it has been urged that the drug be given three times a week; that soda be given simultaneously; that the intake of water be high; that dextrose be given freely first, to saturate the liver with glycogen, thus enabling it to resist the effects of a toxin; that iodine be not given simultaneously, and that the derivative neocinchophen (ethyl ester of *para*-methylphenylcinchoninic acid) be used. However, in spite of these precautions, toxic jaundice continues to occur.

CASES REPORTED ELSEWHERE THAN FROM THE MAYO CLINIC

In 1923, Worster-Drought reported the case of a man, aged 59, with chronic gout, who had used cinchophen in doses of 7½ grains (0.5 Gm.) three times daily for twelve days; urticaria developed and then cleared. Three weeks later, after another dose of cinchophen, urticaria recurred, and in ten days jaundice developed and did not clear for several weeks. The icterus was of moderate degree, and enlargement or tenderness of the liver was not demonstrable.

In 1925, Cabot and Cabot[14] reported the case of a man, aged 42, who had never been strong since the occurrence of typhoid fever in his youth. He had indefinite pains in his arms and legs for several years, and fatigue and weakness for one year. In the preceding two months he had used 3 packages of Weldona. Dull, burning retrosternal pain and belching developed, and were followed by progressive jaundice. Vomiting followed, and later edema and ascites. After vomiting much blood the patient became irrational and comatose, and died about six weeks after the onset of jaundice. At necropsy esophageal varices were found. The liver weighed 780 Gm., and had undergone yellow atrophy.

In 1926, Brown[15] (details given by Graham[16]) reported 2 cases.

Case 1.—A woman, aged 69, had used 170 grains (11 Gm.) of cinchophen weekly for ten weeks for pains in the joints. Anorexia, vomiting and then jaundice developed. The jaundice deepened; the patient became very ill, and died on the eighth day. At necropsy the liver was small and was the site of advanced chronic hepatitis.

Case 2.—A woman, aged 36, used atoquinol in varying doses for five months for infectious arthritis, taking in all about 2,330 grains (151 Gm.). Jaundice developed, and death occurred ten days after her dismissal from the hospital. Necropsy was not made.

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14. Cabot, R. C., and Cabot, Hugh: Case Records of Massachusetts General Hospital: Case 11231; Acute Yellow Atrophy, Boston M. & S. J. **192**:1122 (June 4) 1925.

15. Brown, W. L.: Atophan Derivatives in Rheumatism: A Caution, Brit. M. J. **2**:37 (July 3) 1926.

In 1927, Graham[16] reported the case of a woman, aged 63, who had used 150 grains (9.75 Gm.) of atophan weekly for rheumatoid arthritis. After three months she began to vomit, but continued to take the drug up to within three weeks before her death. Jaundice was present the last four days and coma the last two days. At necropsy the liver was small and revealed the presence of severe chronic hepatitis.

In 1926, Evans[17] reported 3 cases, but did not give the age and sex of the patients. Jaundice developed after 225 grains (15 Gm.) of atophan had been taken by each. In the first case jaundice recurred after from 7½ to 15 grains (0.5 to 1 Gm.) of atophan had been taken. All the patients recovered.

In 1926, Glover[18] reported the case of a woman, aged about 60, who received 38.5 cc. of atophanyl intravenously in varying amounts and at varying intervals for arthritis. Jaundice developed five days after the last injection and cleared in one month.

In 1926, Willcox[19] reported the case of a man, aged 69, who used 5 grains of atophan (0.3 Gm.) three times a day for a week for chronic gout. In a few days rapidly deepening jaundice developed, which persisted until the patient's death, twenty-eight days later. The terminal symptoms were those of icterus gravis. No mention was made of necropsy. Two other cases of jaundice occurring after the use of atophan, with recovery of the patients, were cited by Willcox, but he did not give further details.

In 1926, Wells[20] reported the case of a woman, aged 63, who, as treatment for arthritis, used twenty 7½ grains (0.5 Gm.) tablets of atophan weekly for from four and a half to five months. After three months of medication, vomiting developed, but the woman continued to use the drug until three weeks before her death. Jaundice was present only the last four days, and coma developed two days before death. At necropsy the liver was small and shrunken, and yellow atrophy was present.

In 1926, Klinkert[21] reported 2 cases, and in 1927,[22] 1 case.

Case 1.—A woman with acute polyarthritis was given 5 cc. of atophanyl daily for fifteen days. Three days later, atophan was given three times a day for one month. On account of some abdominal pain, the medicine was omitted for a few days and then given twice daily for one month. A total of 166 tablets was taken. Malaise, anorexia and biliuria then developed. The liver was enlarged. The patient recovered.

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16. Graham, George: The Treatment of Gout, Proc. Roy. Soc. Med. (Sect. Therap. & Pharmacol.) **20**:1 (Jan.) 1927.

17. Evans, Geoffrey: Atophan Derivatives in Rheumatism, Brit. M. J. **2**:93 (July 10) 1926.

18. Glover, L. G.: Atophan-Derivatives in Rheumatism, Brit. M. J. **2**:136 (July 17) 1926.

19. Willcox, W. H.: Atophan Derivatives in Rheumatism, Brit. M. J. **2**:273 (Aug. 7) 1926.

20. Wells, C. J. L.: Atophan Derivatives in Rheumatism, Brit. M. J. **2**:759 (Oct. 23) 1926.

21. Klinkert, D.: Gelbsucht als Folge längeren Gebrauchs von Atophan, Therap. d. Gegenw. **67**:334, 1926.

22. Kinkert, D.: Gelbsucht als Folge längeren Gebrauches von Atophan, Klin. Wchnschr. **6**:24 (Jan. 1) 1927.

CASE 2.—A woman, aged 55, took 140 tablets of atophan, following which anorexia and urobilinuria developed, which lasted for one month, but biliuria did not result, and the patient recovered.

CASE 3.—A man, aged 60, with acute polyarthritis, took 160 tablets of atophan (1,200 grains, or 80 Gm.). A month later painless jaundice developed and rapidly deepened, but it finally cleared in two and a half months. The liver was palpable and slightly tender.

In 1927, Kingreen [23] reported the case of a woman, aged 31, who had biliary colic for two years and a small tumor below the liver, which was enlarged. She was given 75 grains (5 Gm.) of biloptin intravenously for cholecystography. The following day cholecystectomy for subacute cholecystitis without stones was performed. Two days later jaundice was noted, and vomiting occurred. The jaundice became deep, but finally cleared in a month.

In 1927, Hitzenberger [24] reported two cases.

CASE 1.—A man, aged 21, with diabetes insipidus was given biloptin for cholecystography because of a complaint of tenderness at the right costal margin. The next day jaundice developed and progressed, and was associated with vomiting, convulsions and coma. Death occurred on the tenth day. Necropsy revealed yellow atrophy of the liver and a tumor of the pituitary gland.

CASE 2.—A man, aged 60, had been given biloptin for cholecystography because of a tumor in the right hypochondrium. The next day jaundice, anorexia, vomiting and pruritus developed. Recovery occurred in ten days.

In 1927, Schwartz [25] reported the case of a woman, aged 30, who received 75 grains (5 Gm.) of biloptin for cholecystography. Following this she complained of some gastric distress, and two days later vomiting and slight jaundice developed. Two weeks later, at the time of the report, the jaundice was deepening. The outcome was not given.

In 1927, Singer [26] reported the case of a woman, aged 56, who complained of vomiting, pain in the right portion of the abdomen and fever. On account of a mass in the right upper abdominal quadrant, biloptin was given for cholecystography. Several hours later severe vomiting began, and the following day jaundice was noticed. The next day hepatic dulness had diminished. During the next few days the jaundice lessened, but later pneumonia developed, and death occurred sixteen days after the administration of biloptin. At necropsy recurring ulcerative mitral endocarditis with hemorrhagic nephritis was found. Death was caused by endocarditis, but it was felt that the jaundice was due to biloptin.

In 1927, Haudek [26] reported the case of a man, aged 30, who received biloptin for cholecystography on account of distress in the region of the gallbladder. This was followed by nausea, vomiting and jaundice. Recovery occurred in three weeks.

In 1927, Rake [27] reported the case of a man, aged 54, who suffered from chronic alcoholism and gout, and who had used more than 1,500 grains (100 Gm.)

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23. Kingreen, Otto: Vorsicht bei der Verabreichung von Dijodatophan (Biloptin), Deutsche med. Wchnschr. **1**:971 (June 3) 1927.

24. Hitzenberger, K.: Acute Leberatrophie nach Biloptin, Wien. klin. Wchnschr. **40**:205 (Feb. 17) 1927.

25. Schwartz, G.: Schweren Ikterus nach "Biloptin," Wien. klin. Wchnschr. **40**:238 (Feb. 17) 1927.

26. In discussion on Schwartz.[25]

27. Rake, G. W.: A Case of Subacute Yellow Atrophy Following the Taking of Atophan, Guy's Hosp. Rep. **77**:229 (April) 1927.

of atophan. One month before Rake saw the patient, sharp pain in the epigastrium had appeared and had been followed by slight jaundice, which had deepened and then gradually cleared. The clinical diagnosis was gallstones. Following another attack of gout, 10 grains (0.65 Gm.) of atophan was given on two days, and vomiting and diarrhea followed. Exploration revealed a small and irregularly shaped liver. No gallstones were found, and the abdomen was closed. Death occurred on the third day after operation. The liver weighed 1,150 Gm. and revealed evidence of necrosis and regeneration.

In 1927, de Rezende [28] reported 3 cases.

Case 1.—A woman, aged 52, used 1,875 grains (125 Gm.) of atophan for rheumatic pains. Painless jaundice developed and persisted for six weeks. Following the subsequent intravenous injection of atophanyl, icterus of mild degree returned, but the patient recovered.

Case 2.—A man had used atophan in small amounts, and intense jaundice and marked loss of weight occurred. He recovered in forty days.

Case 3.—A woman, aged 52, with sciatica of the left leg used from 20 to 40 capsules of atophan (270 grains, or 18 Gm.). Later more atophan was used, and jaundice developed. The patient recovered in one month.

In 1928, Rabinowitz [29] reported 2 cases.

Case 1.—A man, aged 33, began to use atophan following the extraction of a tooth, and took 1,500 grains (100 Gm.) in three months. Three weeks after the conclusion of the three months nausea, anorexia and weakness developed, and a week later, painless jaundice, which later became intense. The concentration of bilirubin was as high as 38 mg. in each 100 cc. of serum, but within two months after the jaundice had first appeared it had decreased to 3 mg. The patient recovered.

Case 2.—A man, aged 39, suffered from "cold in the back." Following the use of 25 tablets of atophan, each of 7½ grains (0.5 Gm.), nausea, and three days later, jaundice and weakness developed. The concentration of bilirubin was 13 mg. in each 100 cc. of serum; in two and a half weeks it decreased to 2.5 mg. The patient recovered in one month.

In 1928, Weil [30] reported the case of a man, aged 47, who used atophan in unknown amounts, following which jaundice developed, the duration of which was not given. Necropsy revealed the presence of yellow atrophy. The pathologist felt that undernutrition was a factor in the development of the jaundice.

In 1928, Klinkert [31] reported the case of a woman, aged 65, who used 4 tablets of atophan daily for a total of 900 grains (60 Gm.) for rheumatic pain. This was followed by anorexia and jaundice of five weeks' duration. The patient recovered.

In 1928, Lowenthal, Mackay and Lowe [32] reported 2 cases.

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28. de Rezende, Cassio: Rheumatismo atophan e ictericia, Brasil-med. **41**:1005 (Sept. 24) 1927.

29. Rabinowitz, M. A.: Toxic Hepatitis and Hepatolysis Following the Use of Atophan, M. Clin. North America **11**:1025 (Jan.) 1928.

30. Weil, Paul: Leberatrophie nach Atophanbehandlung? Ein Obergutachten, Med. Welt **2**:257 (Feb. 18) 1928.

31. Klinkert, D.: Atophantherapie und Leber, Therap. d. Gegenw. **69**:140, 1928.

32. Lowenthal, L. J. A.; Mackay, W. A., and Lowe, E. C.: Two Cases of Acute Yellow Atrophy of the Liver Following Administration of Atophan, Brit. M. J. **1**:592 (April 7) 1928.

Case 1.—A woman, aged 55, took 7½ grains (0.5 Gm.) of atophan daily for six months because of arthritis (2,700 grains, or 175.5 Gm.). Deepening jaundice, delirium and coma then developed. The woman died six days after the onset of jaundice. Necropsy revealed yellow atrophy of the liver; the organ weighed 538 Gm.

Case 2.—A woman, aged 55, who had rheumatic pain received 7½ grains (0.5 Gm.) of atophan three times a day over a period of about two months, or a total of 540 grains (35.1 Gm.). Two weeks later rapidly progressive jaundice developed, with some tenderness over the gallbladder. On account of the uncertain diagnosis, exploration was made, and a small cirrhotic appearing liver was found. Death occurred the next day, three weeks after the onset of jaundice. Necropsy revealed yellow atrophy, and the liver weighed 744 Gm.

In the London letter[33] in *The Journal of the American Medical Association*, the case was reported of a woman, aged 55, who received atophan three times daily for three weeks, a total of 525 grains (35 Gm.). After five weeks of jaundice, death occurred. Necropsy revealed yellow atrophy.

In 1928, Sutton[34] reported the case of a woman, aged 27, who used atophan for arthritis (75 tablets). This was followed by weakness, nausea, vomiting, edema, ascites and jaundice of eight weeks' duration. Necropsy disclosed yellow atrophy.

In 1929, Dassen[7a] reported 2 cases.

Case 1.—A woman, aged 29, received an unknown amount of cinchophen and sodium salicylate for rheumatic fever. Two days later sore throat with phlegmon developed, and then jaundice became noticeable. The patient gradually recovered.

Case 2.—A woman with mercurial toxic hepatitis and marked jaundice received atophanyl intravenously, which markedly aggravated the jaundice. Recovery was slow, but was complete in three months.

In 1929, Motzfeldt[35] reported the case of a woman, aged 27, who received 1,755 grains (117 Gm.) of cinchophen in two periods for two months. Jaundice developed, but the patient recovered slowly in two months.

In 1929, Braun[36] reported the case of a woman, aged 55, who received 5 cc. of atophanyl intravenously daily for twenty-five days. This was followed by jaundice, ascites, edema and enlargement of the liver. Recovery occurred; the duration of the illness was not given.

In 1929, Frenzel[37] reported the case of a man, aged 55, who used from 5 to 7 tablets, each of 7½ grains (0.5 Gm.), of atophan a day for two days (about 90 grains, or 6 Gm.). Marked weakness, emotional disturbance and loss of voice developed, and on the following day jaundice appeared. Later all of these symptoms gradually disappeared, and in three weeks the patient recovered.

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33. London Letter: The Danger of Atophan, J. A. M. A. **90**:1229 (April 14) 1928.

34. Sutton, D. C.: Acute Yellow Atrophy of the Liver Following the Taking of Cinchophen: Report of a Case, J. A. M. A. **91**:310 (Aug. 4) 1928.

35. Motzfeldt, K.: Cinchophen and Jaundice, Norsk mag. f. lægevidensk. **90**:283 (March) 1929.

36. Braun, L. I.: Jaundice with Ascites, Due to Intravenous Atophanyl Injections, J. M. A. South Africa **3**:157 (March 23) 1929.

37. Frenzel, W. C.: Liver: Subacute Yellow Atrophy Due to Cinchophen Poisoning: Report of a Case, Wisconsin M. J. **28**:264 (June) 1929.

In 1929, Anderson and Teter [38] reported the case of a woman, aged 48, who received 600 tablets of oxyliodide, of 3 grains (0.2 Gm.) each, in eight months, following which edema, jaundice, ascites and albuminuria developed. She became irrational, convulsions occurred, and death ensued. Necropsy revealed yellow atrophy and a liver weighing 450 Gm. The duration of the jaundice was not stated, but it was probably less than a month.

In 1929, Reichle [39] reported 2 cases.

Case 1.—A woman, aged 20, on account of acute arthritis used cinchophen for three or four months, which was followed by jaundice, with recovery after six weeks. A month later, on account of the recurrence of the arthritis, she used 80 tablets of cinchophen, 7½ grains (0.5 Gm.) each, and 40 tablets of oxyliodide; still later she took 60 grains (4 Gm.) of cinchophen. The symptoms included fever, nausea, vomiting, diarrhea, bleeding from the nose and gums, pain in the thorax, apathy, weakness, emaciation, a macular cutaneous rash, jaundice and coma. The liver and spleen were enlarged. At necropsy the liver weighed 1,950 Gm., and yellow atrophy was present.

Case 2.—A woman, aged 46, with arthritis used cinchophen in large amounts, 3,150 grains (204.75 Gm.) in 1926, 2,100 grains (136.5 Gm.) in 1927, and 1,800 grains (117 Gm.) in 1928. Epigastric pain, tenderness, weakness and jaundice developed; later edema, confusion, muscular twitching, convulsions and coma ensued. Death occurred after jaundice of ten or twelve days' duration. Necropsy revealed yellow atrophy and a liver weighing 757 Gm.

In 1929, Liedberg [40] reported 2 cases.

Case 1.—A man, aged 60, used 338 grains (22.5 Gm.) of atophan in three weeks, which was followed by nausea, malaise and jaundice. The liver was enlarged. During the first week, the jaundice increased. This subsequently decreased, with recovery in four weeks.

Case 2.—A woman, aged 63, used 3 tablets of atochinol daily for six weeks for arthritis. Two days after beginning medication, dark urine was noticed. Later dyspepsia, vomiting and jaundice developed. Recovery occurred in one month.

In 1930, Fink [41] reported the case of a man, aged 47, who used 7½ grains (0.5 Gm.) of cinchophen four times daily for arthritis (a total of 180 grains, or 12 Gm.). Three weeks later urticaria developed, and a week later painless jaundice with marked pruritus and purpura developed. The liver was slightly tender. The concentration of bilirubin was 7.5 mg. in each 100 cc. of serum. The jaundice cleared in ten days.

In 1930, Tak [42] reported the case of a man, aged 45, who received 150 grains (10 Gm.) of atophan. Later he took another 45 grains (3 Gm.), which was followed by anorexia, enlargement of the liver and jaundice. Recovery occurred in six weeks.

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38. Anderson, S. D., and Teter, D. P.: Acute Yellow Atrophy of the Liver Following Administration of Oxyl Iodide, J. A. M. A. **93**:93 (July 13) 1929.

39. Reichle, H. S.: Toxic Cirrhosis of Liver Due to Cinchophen, Arch. Int. Med. **44**:281 (Aug.) 1929.

40. Liedberg, Nils: Atophan Icterus, Hygiea **91**:801 (Dec. 15) 1929.

41. Fink, A. I.: Cinchophen Poisoning in Allergic Individuals: Report of Two Cases, J. Allergy **1**:280 (March) 1930.

42. Tak, P.: Dangers of Atophan, Nederl. tijdschr. v. geneesk. **74**:1744 (April 5) 1930.

In 1930, Rabinowitz [43] reported 7 cases.

Case 1.—A woman, aged 37, used 360 grains (24 Gm.) of cinchophen for two months for rheumatic pains in the feet. Jaundice developed and persisted for two months. The patient recovered.

Case 2.—A woman, aged 31, used 150 grains (10 Gm.) of atophan for two or three weeks. Weakness and jaundice developed, and because of this complication in the presence of pregnancy, therapeutic abortion was done. The liver was enlarged. The patient recovered from the jaundice in seven weeks.

Case 3.—A man, aged 45, received 7½ grains (0.5 Gm.) of atophan three times daily for four or five months. He lost much weight, and jaundice developed. Ascites was present, and death occurred ten days later. Necropsy revealed portal cirrhosis and a liver weighing 1,100 Gm.

Case 4.—A woman, aged 51, received 450 grains (30 Gm.) of atophan during four weeks. Pain in the abdomen, edema, jaundice and coma developed. Death occurred in four or five days. Necropsy revealed the presence of yellow atrophy.

Case 5.—A woman, aged 26, received 67½ grains (4.5 Gm.) of atophan for pains in the joints, and jaundice developed after tonsillectomy. Later, hyperpyrexia was present. Death occurred ten days after the onset of jaundice. Necropsy was not performed.

Case 6 (also reported by Grolnick [44]).—A woman, aged 45, used Weldona in two courses for about two weeks. This was followed by backache, belching, epigastric distress, diarrhea and malaise, and later by jaundice, which persisted for five weeks. Recovery occurred.

Case 7.—A woman, aged 39, used atophan in large amounts for six months. Progressive jaundice developed. Exploration was made, and the patient died on the operating table. Necropsy revealed that the liver was small and cirrhotic.

In 1930, Lambert [45] reported the case of a man who used Harrell's rheumatism cure in large amounts for from one and a half to two years for rheumatic pains. This was followed by anemia, jaundice of unstated duration and death. Necropsy was not mentioned.

In 1931, Parsons and Harding [46] reported 4 cases.

Case 1.—A woman, aged 65, used Van Ard's rheumatism cure for four months (700 grains or 45.5 Gm. of cinchophen) for chronic arthritis. Progressive weakness, malaise and nausea developed. Vomiting, bloody diarrhea and edema of the ankles were later symptoms. The duration of the jaundice was not known, but it was present one week before death. Coma developed, and death occurred four weeks after the first symptoms. At necropsy yellow atrophy was present, and the liver weighed 450 Gm.

Case 2.—A woman, aged 67, had three mild attacks of jaundice during the use, in unknown amounts, of Van Ard's rheumatism cure for a general "bad feeling." Weakness, headache, nausea, vomiting, progressive jaundice and coma developed. Death occurred on the seventh day after the onset of jaundice. Necropsy revealed that the liver weighed 720 Gm., and yellow atrophy was present.

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43. Rabinowitz, M. A.: Atrophy of the Liver Due to Cinchophen Preparations, J. A. M. A. **95**:1228 (Oct. 25) 1930.

44. Grolnick, Max: Toxic Hepatitis Due to Cinchophen Containing Patent Medicine, M. J. & Rec. **132**:240 (Sept. 3) 1930.

45. Lambert, Alexander, in discussion on Rabinowitz.[43]

46. Parsons, Lawrence, and Harding, W. G., Jr.: Cinchophen (Atophan) Poisoning: Report of Four Cases, Am. J. M. Sc. **181**:115 (Jan.) 1931.

Case 3.—A woman, aged 40, used atophan (1,950 grains or 127 Gm.) for six months because of rheumatism. Epigastric pain, nausea, vomiting, edema, marked jaundice and localized convulsions developed. Death occurred on the eighth day. Necropsy revealed yellow atrophy and a liver weighing 735 Gm.

Case 4.—A woman, aged 46, used Cass' rheumatism cure in unknown amounts for an unknown period because of arthritis. Malaise, mild jaundice which progressed, nausea, vomiting and confusion developed. Death occurred on the ninth day after the onset of symptoms. At necropsy the liver weighed 700 Gm.

In 1931, Walker [47] reported 2 cases.

Case 1.—A man, aged 43, used 96 grains (6.24 Gm.) of cinchophen for post-traumatic pain in the leg. A month later anorexia and epigastric distress developed, and in a few days vomiting and jaundice. These symptoms progressed, coma developed, and death occurred eleven days after the onset of jaundice. Necropsy revealed that the liver weighed 850 Gm. and that yellow atrophy was present.

Case 2.—A woman, aged 59, six months before the presenting illness had used 750 grains (48.75 Gm.) of cinchophen on account of arthritis. Because of recurring pains, she again used cinchophen (30 tablets of 7½ grains each), which immediately produced heartburn, nausea and anorexia. A week later jaundice, persistent vomiting and drowsiness developed. After another week the liver seemed to decrease in size, and there was some epigastric tenderness. The jaundice deepened, the patient became delirious and stuporous, and edema developed. Death occurred two weeks after the onset of jaundice. At necropsy the liver weighed 650 Gm.; necrosis of the hepatic cells with regeneration was also noted.

In 1931, Ross [48] reported 5 cases.

Case 1.—A woman, aged 42, used unknown amounts of tolysin intermittently for pains in the joints and muscles. A month later a severe digestive upset occurred, with pain, vomiting and fever, followed by jaundice. The vomiting continued, and there was evidence of a decreased area of hepatic dulness, delirum, ascites and petechial hemorrhages. Death occurred two months after the onset of jaundice. Necropsy revealed that the liver weighed 670 Gm., and that necrosis and regeneration were present.

Case 2.—A woman, aged 58, used quinophen in doses of from 10 to 15 grains (0.65 to 1 Gm.) daily for several weeks on account of attacks of digestive disturbance and epigastric tenderness. Then a severe attack of indigestion and vomiting occurred, followed by jaundice, which persisted. One month and two months later similar attacks occurred, and after the last attack a mass was found at the right costal margin. At operation the gallbladder, which contained stones, was removed, and the common bile duct was drained. Death occurred twelve hours later, two months after the onset of jaundice. At necropsy the liver weighed 750 Gm.; necrosis of the hepatic cells with some regeneration was found.

Case 3.—A man, aged 41, with tuberculosis of the right hip of two years' duration, used cinchophen and tolysin intermittently for three months. Death occurred

47. Walker, W. G.: Cinchophen and Acute Yellow Atrophy of the Liver: Report of Two Cases, New England J. Med. **204**:253 (Feb. 5) 1931.

48. Ross, J. B.: Liver Damage Following Cinchophen Preparations, with a Report of Five Cases, Canad. M. A. J. **24**:632 (May) 1931.

forty-eight hours after operation on the hip. There was evidence of a decreased area of hepatic dulness, but jaundice was absent. Necropsy revealed that the liver weighed 1,220 Gm., and was necrotic.

Case 4.—A man, aged 26, took neocinchophen irregularly for two weeks for pains in the joints and muscles. During the last three weeks he had lost weight and had become slightly jaundiced; glycosuria developed, which eventually disappeared. Recovery occurred in from four to five months.

Case 5.—A man, aged 68, used 7½ grains (0.5 Gm.) of atophan three times a day. A total of 855 grains (55 Gm.) was taken. This was followed by slight digestive disturbance, vomiting and jaundice. He recovered in from one to two weeks.

In 1931, Sherwood and Sherwood [49] reported the case of a man, aged 27, who used 75 grains (5 Gm.) of atophan for arthritis of possibly gonorrheal origin. Five days later mild jaundice developed, which cleared in one month.

In 1931, Willcox [50] reported 4 cases.

Case 1.—A man, aged 35, used 2 tubes of atophan for from six to eight weeks. A month later deep jaundice developed, which persisted until recovery two months later.

Case 2.—A man, aged 69, used 5 grains (0.3 Gm.) of atophan three times a day for six days. Three weeks later jaundice and enlargement of the liver developed. Death occurred about four weeks after the onset of jaundice. Necropsy was not mentioned.

Case 3.—A woman, aged 20, used Gorum cachets twice daily for six days. Three weeks later rapidly deepening jaundice developed; five weeks later ascites was noted, and three weeks later severe hematemesis occurred, with death in two days, two months after the onset of jaundice. Necropsy was not mentioned.

Case 4.—A woman, aged 52, used Gorum cachets three times a day intermittently for five weeks. A month later rapidly deepening jaundice developed, associated with vomiting and an enlarged liver. Recovery occurred in two months.

In 1931, Cabot [51] reported the case of a woman, aged 71, who used farastan for several weeks on account of arthritis. This caused diarrhea. Weakness, edema, ascites and slight icterus developed. Death occurred about ten days after the development of edema. Necropsy revealed a liver weighing 800 Gm. and the characteristic picture of yellow atrophy.

In 1931, Eimer [52] reported the case of a man, aged 52, who used 1,770 grains (118 Gm.) of atophan during forty days for subacute arthritis. A month after he began to use the drug, malaise, anorexia, slight jaundice and fever developed. Later petechiae developed, associated with marked deepening of the jaundice, enlargement of the liver and general apathy. Recovery occurred in seven weeks.

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49. Sherwood, K. K., and Sherwood, H. H.: Acute Toxic Hepatitis (Acute Yellow Atrophy) Due to Cinchophen: Report of a Case, Arch. Int. Med. **48**:82 (July) 1931.

50. Willcox, William: Toxic Jaundice, Lancet **2**:57 (July 11) 1931.

51. Cabot, R. C.: Case Records of Massachusetts General Hospital: Case 17291; Four Months' Pain in the Legs and Five Days' Edema Below the Waist, New England J. Med. **205**:153 (July 16) 1931.

52. Eimer, Karl: Atophanvergiftung und ihre Behandlung, Deutsche med. Wchnschr. **57**:1663 (Sept. 25) 1931.

In 1931, Bogen[53] reported the case of a girl, aged 19, who received 7½ grains (0.5 Gm.) of cinchophen three times a day for five weeks (825 grains or 55 Gm.) on account of arthritis of the ankle. Nausea, vomiting and discomfort in the right upper quadrant of the abdomen developed, and a week later definite jaundice was noted. The concentration of bilirubin was 15 mg. in each 100 cc. of serum. A week later, on account of severe pain in the right side of the abdomen, nausea, vomiting and leukocytosis, exploration of the abdomen was undertaken under spinal anesthesia. Aside from a distended stomach, the findings were negative. Death occurred in five days, twelve days after the onset of jaundice. Necropsy revealed a necrotic liver weighing 1,200 Gm.

In 1931, Elliot[54] reported the case of a woman, aged 24, who used 126 grains (8.4 Gm.) of oxyliodide for a stiff, painful shoulder; nausea, vomiting, rapidly deepening jaundice, mental confusion and coma developed. Hallucinations, disorientation and Babinski reflexes were present. Death occurred on the twelfth day after the onset of symptoms. Necropsy was not mentioned.

In 1932, Gargill[55] reported 2 cases.

Case 1.—A woman, aged 47, received 84 grains (5.6 Gm.) of oxyliodide for chronic arthritis. Moderate pruritus developed; later anorexia and nausea appeared, and two weeks later jaundice developed. The liver was enlarged, and the concentration of bilirubin was 26 mg. in each 100 cc. of serum. Recovery occurred in two months.

Case 2.—A woman, aged 47, used 432 grains (28.8 Gm.) of atophan and oxyliodide in two weeks for pain in the left leg. One week later pruritus, anorexia, nausea and jaundice were noted. The liver was enlarged. The patient recovered in three months.

In 1932, Lind[56] reported the case of a woman, aged 39, who following the extraction of a tooth took from 10 to 12 tablets (7½ grains or 0.5 Gm. each) of cinchophen. This was followed by weakness, and five weeks later gradually deepening jaundice developed. A week later still the jaundice decreased, and then ascites developed for which paracentesis was required on three occasions. Death occurred five weeks after the onset of jaundice. Necropsy revealed yellow atrophy of the liver, which weighed 750 Gm.

In 1932, S. Weiss[7c] reported 3 cases in which acute necrosis of the liver developed after the use of icterosan (10 per cent atophan) for advanced jaundice. The age and sex of the patients are not given.

In 1932, C. R. Weis[57] reported 3 cases.

Case 1.—A man, aged 26, used 60 grains (4 Gm.) of atophan daily for three months because of rheumatic pains following tonsillitis. Jaundice developed, associated with nausea, vomiting, edema, lethargy and delirium. Death occurred

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53. Bogen, Emil: Cinchophen Poisoning: Report of Case, California & West. Med. **35**:269 (Oct.) 1931.

54. Elliot, A. H.: Toxic Cirrhosis of the Liver from "Oxyl-Iodide": Report of Case, J. A. M. A. **97**:1384 (Nov. 7) 1931.

55. Gargill, S. L.: Cinchophen Poisoning: A Report of Three Cases, New England J. Med. **206**:183 (Jan. 28) 1932.

56. Lind, S. C.: Report of a Case of Acute Yellow Atrophy of the Liver Due to the Use of a Small Amount of Cinchophen, Ohio State M. J. **28**:28 (Jan.) 1932.

57. Weis, C. R.: Toxic Cirrhosis of the Liver Due to Cinchophen Compounds: Report of Three Fatal Cases, J. A. M. A. **99**:21 (July 2) 1932.

after three weeks. Necropsy revealed yellow atrophy of the liver; the organ weighed 680 Gm.

Case 2.—A man, aged 65, used 60 grains (4 Gm.) of atophan daily for four months for arthritis. Weakness, anorexia, nausea and drowsiness developed, followed in a few days by vomiting and jaundice. Later on, edema, delirium and coma developed. Death occurred about three weeks after the onset of symptoms. At necropsy there was necrosis of the liver with some signs of regeneration.

Case 3.—A woman, aged 64, used 4 tablets of farastan daily for four months on account of arthritis. Nausea, vomiting, anorexia, weakness and rapidly deepening jaundice developed. Death occurred about two weeks after the onset of symptoms. Necropsy revealed a small, extensively necrosed liver.

In 1932, Berger and Schweid [58] reported 2 cases.

Case 1.—A woman, aged 63, used 540 grains (35 Gm.) of cinchophen for arthritis. A digestive upset, slight pain in the upper quadrant of the abdomen and jaundice developed. The jaundice increased, and was associated with a decrease in the size of the liver, pruritus, drowsiness and muscular twitching. Six weeks later her condition was much improved. Exploration was undertaken because of a mass in the right upper abdominal quadrant. Peritonitis with death followed. At necropsy the liver weighed 940 Gm., and yellow atrophy was present.

Case 2.—A man, age unknown, used 1,417 grains (92 Gm.) of cinchophen in three weeks, which was followed by rapidly deepening jaundice, a decrease in the size of the liver, muscular twitching and coma. Necropsy was not reported.

In 1932, Reah [59] reported 3 cases.

Case 1.—A woman, aged 64, used 588 grains (38 Gm.) of cinchophen at intervals. This was followed by nausea, anorexia, vomiting, jaundice, pruritus and giddiness. Death occurred twenty-five days after the onset of jaundice. Necropsy revealed red atrophy of the liver.

Case 2.—A man, aged 63, used 60 grains (4 Gm.) of cinchophen because of gout. Fifteen weeks later abdominal pain, vomiting and jaundice developed. Coma and death followed three weeks after the onset of jaundice. At necropsy the liver was found to be small, with extensive necrosis.

Case 3.—A woman, aged 39, used 7 grains (0.45 Gm.) of cinchophen three times daily for two months. Severe pain in the lower part of the abdomen, vomiting, headache, thirst and jaundice developed. The patient recovered.

In 1932, Parsons and Harding [60] reported 6 cases.

Case 1.—A woman, aged 64, used Renton's hydrocine, 6 tablets daily for six months (5,400 grains or 351 Gm. of cinchophen). This was followed by deep jaundice, a decreasing area of hepatic dulness, slight edema and distention of the abdomen. Four months later, marked ascites, edema and distention of the superficial abdominal veins developed. Paracentesis was necessary on several occasions. Six weeks later omentopexy and posterior gastro-enterostomy were performed for pyloric obstruction. Death occurred in three days, six months after the onset of jaundice. Necropsy was not made.

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58. Berger, S. S., and Schweid, H. H.: Cinchophen Poisoning in a Diabetic with Induction of Hypoglycemia, M. J. & Rec. **136**:50 (July 20) 1932.

59. Reah, T. J.: Cinchophen Poisoning, Lancet **2**:504 (Sept. 3) 1932.

60. Parsons, Lawrence, and Harding, W. G., Jr.: Fatal Cinchophen Poisoning: Report of Six Cases, Ann. Int. Med. **6**:514 (Oct.) 1932.

CASE 2.—A man, aged 70, used 45 tablets of Renton's rheumatism remedy in a month (225 grains or 14.6 Gm. of cinchophen) because of rheumatism. Much pruritus developed; later progressive weakness, loss of weight, jaundice and a decreasing area of hepatic dulness with tenderness appeared. The symptoms progressed, and death occurred four weeks after the onset of jaundice. Necropsy was not made.

CASE 3.—A woman, aged 64, used 12 tablets of Renton's hydrocine for arthritis. Three months later jaundice associated with decreasing hepatic dulness developed, which later was followed by coma. The concentration of bilirubin was 25 mg. in each 100 cc. of serum. Death occurred two weeks after the onset of jaundice. Necropsy revealed a necrotic liver weighing 500 Gm.

CASE 4.—A man, aged 56, used atophan for three or four weeks because of pain in the foot. Generalized pruritus developed and then subsided. Six months later jaundice, weakness and anemia developed. The jaundice subsided for a time, but recurred. Death occurred more than six months after the use of the drug. Necropsy was not made.

CASE 5.—A man, aged 62, used 6 tablets of atophan daily for three weeks on account of neuritic pains in the legs. This was followed by urticaria and marked jaundice, which progressed and led to death. The duration of the jaundice was not given, and necropsy was not performed.

CASE 6.—A man, aged 43, used 200 of Renton's hydrocine tablets in a period of six months (1,000 grains or 65 Gm. of cinchophen) for arthritis of the hips. Epigastric distress, tenderness, vomiting and rapidly deepening jaundice occurred. The symptoms progressed to a fatal outcome. The duration of the jaundice is not given. At necropsy a necrotic liver weighing 780 Gm. was found.

In 1932, Davis [12] reported 3 cases.

CASE 1.—A woman, aged 45, received atophan and neocinchophen in large doses for a year because of infectious arthritis. Jaundice developed and death occurred in a few days. Necropsy was not made.

CASE 2.—A girl, aged 17 years, with a history of catarrhal jaundice two years previously, received 10 grains (0.65 Gm.) of tolysin four times daily, or a total of 700 grains (45.5 Gm.), because of infectious arthritis. Jaundice of a rapidly progressive type developed three weeks after she started to use the drug, and was associated with delirium and hyperpyrexia. Death occurred in eight days. Necropsy was not performed.

CASE 3.—A patient, age and sex unknown, received cinchophen and potassium iodide alternately. Three weeks later jaundice developed. Recovery occurred.

In 1932, MacGregor [61] reported the case of a man, aged 58, who had previously used alcohol heavily and had had diabetes mellitus for four years. On account of headache and painful joints and muscles, he was given 5 grains (0.3 Gm.) of neocinchophen three times a day (total amount unknown, but the prescription was filled several times). Jaundice developed and was associated with weakness, nausea, vomiting, drowsiness, restlessness and coma. Death occurred in ten days. Necropsy was not made.

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61. MacGregor, D. A.: Cinchophen Poisoning, Proc. Staff Conf., Wheeling Clin. **3**:46 (Sept. 1) 1932.

CASES FROM THE MAYO CLINIC

Group 1 is composed of cases in which there was no jaundice.

CASE 1.—A man, aged 66, registered at the clinic on July 6, 1932. He had had lumbago three or four times in the previous twelve years, and constant lumbar pain, with radiation into the posterior portion of both thighs, for which he had taken 4 or 5 boxes (each containing 24 tablets) of atophan in the previous four or five years, and 3 or 4 boxes (each containing 24 tablets) of cinchophen in the previous two or three years, with a great deal of relief. He had used only a little alcohol.

The lower edge of the liver was palpable 6 cm. below the costal margin; ascites and collateral veins were absent. The movements of the spine were limited. The concentration of bilirubin was 1.8 mg. in each 100 cc. of serum, and the van den Bergh reaction was indirect. The bromsulphthalein test of hepatic function revealed retention of dye, graded 3. The galactose tolerance test was negative. Roentgenologic examinations of the gallbladder revealed no abnormality; those of the spinal column gave evidence of hypertrophic changes in the lumbar portion. The diagnosis was toxic cirrhosis due to cinchophen and hypertrophic arthritis with sciatic pain. The patient was given a sacro-iliac belt and instruction in physical therapy. A diet high in carbohydrates was recommended, and he was advised not to use cinchophen and asked to return for reexamination. On November 16, the liver was definitely decreased in size, its surface was smooth, and its edge was soft. The retention of dye had diminished to grade 1, the concentration of bilirubin was 1.2 mg., and the van den Bergh reaction was indirect.

CASE 2.—A woman, aged 54, entered the clinic on July 4, 1932. For the previous ten years she had been treated for hypertension, indigestion and constipation. In April, 1932, she took 120 capsules of oxyliodide of 3 grains (0.2 Gm.) each because of rheumatic pain. The first of a series of attacks of weakness of several hours' duration, without change in the pulse rate, blood pressure, color, respiration or sweating, suddenly appeared three weeks previous to admission. Six days afterward an atypical attack of pain involved the entire abdomen.

On examination, the blood pressure in millimeters of mercury was 125 systolic and 80 diastolic, and a slight resistance in the right upper quadrant of the abdomen was noted. The retinal vessels gave evidence of hypertensive sclerosis, graded from 1 to 2. A galactose tolerance test and studies of the stools for parasites, ova and occult blood gave negative results. The electrocardiogram was normal. Roentgenograms of the stomach disclosed nothing significant; those of the gallbladder revealed that the organ was not functioning. The concentration of bilirubin was 2.3 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. The bromsulphalein test of hepatic function disclosed a retention of dye, graded 4. The diagnosis was hypertension, arteriosclerosis, toxic cirrhosis due to cinchophen, and constipation. Possibly cholecystitis existed, but this did not explain satisfactorily the hepatic injury and other symptoms. The decision as to the advisability of operation was deferred until the results of the disappearance of the jaundice and the return of the hepatic function to normal had been observed. It was uncertain whether the attacks of weakness were an expression of myocardial degeneration or of disease of the liver. The patient was placed on a diet high in carbohydrates, including dextrose in large amounts, and was dismissed on July 26. The patient wrote on November 10, stating that she had gained weight, was much improved and felt well.

Comment.—Cases 1 and 2 represent latent or mild forms of toxic cirrhosis caused by cinchophen without visible jaundice. In case 1, the enlargement of the liver led to a search for etiologic factors, and a history of the use of the drug was obtained. No elevation of the concentration of bilirubin in the serum or change in the van den Bergh reaction was present. Hepatic injury was revealed by the enlargement of the liver and by the retention of dye. The decrease in the size of the liver, its softer consistence and the improvement in function as measured by the retention of dye, as noted on subsequent examination, served to confirm our original opinion that the diagnosis was toxic cirrhosis caused by cinchophen poisoning instead of portal cirrhosis. In case 2, a subclinical degree of icterus was present. Only after repeated questioning as to the cause of the weakness and peculiar abdominal symptoms was a history of the use of the drug elicited and laboratory evidence of hepatic injury obtained. The improvement with discontinuation of the drug and appropriate treatment indicates that not only cholecystitis, but likewise myocardial degeneration, was a relatively insignificant factor. Toxic cirrhosis due to cinchophen satisfactorily explains the syndrome. The danger of operation in such cases can be avoided only by careful consideration of all factors. Similar cases have been reported by Ross and Klinkert. In the case reported by Ross, an atrophied liver (1,220 Gm.) was found at necropsy; death had occurred after an operation on a tuberculous hip. Definite hepatic injury without jaundice had occurred. In Klinkert's case urobilinuria of thirty days' duration was noted. Jones [62] stated that he had seen 1 case of diffuse hepatic disease without jaundice, and 4 or 5 cases of yellow atrophy of unstated cause with ascites as a presenting symptom. Such cases definitely establish the fact that hepatic injury without jaundice occurs and presents clinical pictures capable of recognition which in many cases no doubt precede the more obvious phases of the disease. Certainly it is at the preicteric stage of toxic cirrhosis that a diagnosis is best made if much disability and permanent hepatic injury are to be avoided, and if complete functional and anatomic restoration is to be accomplished.

Group 2 is composed of cases in which there was mild jaundice.

CASE 3.—A man, aged 52, registered at the clinic on Sept. 29, 1930. For seven months he had suffered from pain in the left sacro-iliac region, with radiation into the region of distribution of the left sciatic nerve. Two months before admission his physician prescribed oxyliodide. Six weeks later jaundice came on gradually, and the administration of oxyliodide was promptly discontinued. During the two weeks before admission there was no evidence that the jaundice was decreasing.

Examination revealed slight icterus. The liver was slightly enlarged and tender. Examination of the spinal column revealed scoliosis, with list to the right, and

62. Jones, Chester, in discussion on Cabot.[51]

neurologically there was evidence of sciatic neuritis on the left side. The van den Bergh reaction was direct, and the concentration of bilirubin was 5.8 mg. in each 100 cc. of serum. When the patient was under treatment for sciatica, the jaundice cleared in two and a half weeks after admission; the concentration of bilirubin was 2.5 mg. in each 100 cc. of serum, and the van den Bergh reaction was still direct.

Case 4.—A man, aged 52, registered at the clinic on Feb. 2, 1931, with the complaints of pains in the joints and jaundice. He had been a moderate user of alcohol, and during the previous nine years he had recurrent attacks of arthritis, which had left no residual changes. Three weeks before admission he had another attack and took 30 tablets of oxyliodide over a period of ten days. Shortly before admission his physician noticed a slight degree of jaundice. He had lost 7 pounds (3.2 Kg.), and he experienced considerable lassitude and weakness.

Examination revealed the presence of a mild grade of icterus. The liver, which was tender, extended 7 cm. below the xiphoid cartilage, and 5 cm. below the costal margin in the right mammary line. The spleen was not palpated. External evidence of previous arthritis was not visible. Roentgenograms of the gallbladder taken after the ingestion of dye revealed that it was not functioning. The concentration of bilirubin was 5.7 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. A bromsulphalein test of hepatic function revealed retention of dye, graded 4. The flow of bile by duodenal drainage was free, 180 cc. being obtained. On February 12, the concentration of bilirubin declined to 2.5 mg. in each 100 cc. of serum. The value for uric acid was 5.2 mg. for each 100 cc. of blood. A diagnosis of gout and toxic hepatitis caused by cinchophen poisoning seemed justified. Decision as to the disease of the gallbladder was deferred until the jaundice cleared, and further roentgenograms of the organ were taken. The patient was dismissed on February 15 on a diet high in carbohydrates with restriction of purines, and was advised to use salicylates and colchicum when necessary for gout. On October 28, roentgenograms of the gallbladder were made elsewhere after the intravenous administration of dye, and the organ was only faintly depicted. A diagnosis of cholecystitis was made, and cholecystecomy was performed on December 9. The surgeon reported that some pericholecystitis was found, as well as inflammatory changes in the mucosa. The significant changes were in the liver; it was almost normal in size, form and consistence, but had a nodular surface. There was distinct cirrhosis, which, however, had not progressed to the stage of producing portal obstruction.

Case 5 (previously reported from the clinical standpoint by Snell and Jordan [63]).—A man, aged 42, registered at the clinic on July 15, 1929. Because of extensive infectious arthritis he had been taking a "rheumatic remedy" that contained cinchophen. Jaundice developed six months previous to examination and still persisted.

The patient was emaciated, moderately jaundiced (concentration of bilirubin, 4.6 mg. in each 100 cc. of serum) and rather badly disabled by infectious arthritis. The liver and spleen were palpable. Ample quantities of bile were secured by duodenal drainage. Discontinuation of treatment with arthritic drugs and a diet high in carbohydrates led to the slow disappearance of the jaundice and recovery from this feature of the illness.

63. Snell, A. M., and Jordan, F. M.: Intrahepatic Jaundice, Northwest Med. **29**:295 (July) 1930.

Comment.—Cases 3, 4 and 5 represent the milder grades of toxic cirrhosis caused by cinchophen. In case 4, the previous use of alcohol raises two questions of importance. Did the alcohol predispose to cinchophen poisoning, and did the alcohol rather than the cinchophen account for the pathologic changes in the liver observed at operation? It is impossible to answer the first question. With regard to the second question, it was observed that although the liver was of almost normal size and consistence, a nodular condition was present. This may be interpreted to mean that the condition was nodular hyperplasia without an obvious increase in connective tissue, a pathologic process at variance with that met in portal cirrhosis, but in keeping with our concept of toxic cirrhosis due to cinchophen. In our opinion, the pathologic changes are best accounted for by cinchophen poisoning, and represent a stage in the pathogenesis of toxic cirrhosis. The differential diagnosis between hepatic disease and cholecystitis in case 4 likewise illustrates some important points. The cholecystitis was too mild and the symptoms were too indefinite to warrant the belief that it was much of a factor in the genesis of the intrahepatic jaundice. The cholecystographic diagnosis of nonfunctioning gallbladder made at the time of the visit to the clinic must be discounted, for cholecystography is of limited value in the presence of jaundice or a diffusely diseased liver. A nonfunctioning gallbladder is often found to be functioning normally when the jaundice has cleared. A normally functioning organ, as indicated by cholecystography, is sometimes seen in the presence of slight jaundice or mild diffuse hepatic disease; in such instances, the test may be considered to have ruled out marked disease of the gallbladder and to have absolved the gallbladder of playing an important part in the causation of the jaundice.

In case 5, the jaundice was of long duration and mild, and it cleared rapidly when the administration of cinchophen was discontinued. The long duration probably depended on the continued administration of cinchophen. The patient evidently had only mild idiosyncrasy to the drug. Malnutrition may have been a predisposing factor that permitted development of the toxic cirrhosis. Few if any symptoms were produced by hepatic injury in cases 3 and 5, and the chief treatment indicated was discontinuance of the use of the drug.

Group 3 is composed of a case in which there was moderately severe jaundice.

Case 6.—A woman, aged 53, first registered at the clinic on Sept. 16, 1929. Subtotal thyroidectomy was performed for exophthalmic goiter of five years' duration. There was no evidence of visceral degeneration. On December 14, the patient returned because of acute scleroderma in the edematous stage, which had developed one month previously. In August, 1930, arthritis appeared, and her physician prescribed cinchophen. Administration of this drug was continued for

five weeks, or until two nights before admission, when she was awakened by pain in the upper part of the abdomen.

The next day the patient was mildly icteric, and slight tenderness was present in the right upper quadrant of the abdomen; the fingers revealed arthritic deformities. The concentration of hemoglobin was 55 per cent. The urine contained tyrosine. The concentration of bilirubin was 10 mg. in each 100 cc. of serum. The retention of dye was graded 4 by the bromsulphalein test. A free flow of bile was obtained by duodenal drainage. Although cholecystography revealed a nonfunctioning gallbladder, this was disregarded because of the jaundice. The patient was placed on a diet high in carbohydrates; calcium lactate was given, and dextrose was administered intravenously. The concentration of bilirubin fluctuated between 11.5 and 14.9 mg. in each 100 cc. of serum until dismissal at the patient's request on September 29. The diagnosis was toxic cirrhosis caused by cinchophen. In October and November, 1931, an exacerbation of the scleroderma necessitated a return to the clinic, but there were no complaints referable to the liver.

Comment.—The condition of the patient in case 6 was moderately severe, without marked constitutional and mental symptoms. The jaundice was deeper and somewhat more prolonged than in the previous group. Digestive disturbances, including pain, were prominent, but under appropriate treatment the patient recovered. The degree and duration of the jaundice approximated those encountered in cases of catarrhal jaundice in which the patients seek hospitalization.

Group 4 is composed of cases in which the patients were convalescent.

Case 7.—A woman, aged 65, entered the clinic on Jan. 20, 1931. She had been in good health, except for rheumatic pains, during the last few years, but had experienced an unexplained loss of 20 pounds (9 Kg.) in the preceding five months. About November 26 she began to take 7½ grains (0.5 Gm.) of cinchophen, three times daily, but this she discontinued at the end of two weeks, after two days' itching of the arms and legs. On December 17, jaundice, without associated chills, fever or pain, appeared, and reached a maximal degree in two days. The patient lost her appetite and was annoyed with belching and bloating. On December 23, she had a severe "gas pain" lasting two hours, with residual aching that lasted for two days, in the right upper quadrant of the abdomen. The jaundice began to improve ten days before the patient's admission to the clinic, and had virtually disappeared three days before, thirty days after the onset.

The sclera and skin were slightly icteric. A cholecystogram revealed that the gallbladder was functioning normally. The concentration of bilirubin was 1.7 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. The bromsulphalein test of hepatic function disclosed retention of dye, graded 2. The diagnosis was toxic cirrhosis due to cinchophen. The patient was dismissed on Jan. 23, 1931.

The woman registered again on May 4. No further trouble had been caused by the liver. The concentration of bilirubin was 1.7 mg. in each 100 cc. of serum, the van den Bergh reaction was indirect, and there was no retention of dye. She had had diarrhea, however, for the last three weeks, and proctoscopic examination revealed early chronic ulcerative colitis.

CASE 8 (previously reported from the clinical standpoint by Comfort [64]).—A man, aged 69, registered at the clinic on Feb. 2, 1932, with the complaint of painless jaundice of one month's duration. In December, 1931, because of arthritis he took 70 capsules of oxyliodide. On Jan. 3, 1932, painless jaundice with clay-colored stools and dark urine developed. The jaundice increased until about January 19, and then began to fade.

General physical examination gave essentially negative results with the exception of jaundice, a loss of 20 pounds (9 Kg.) and a slightly enlarged liver. There was a slight trace of bile in the urine. The concentration of bilirubin was 10 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Duodenal drainage yielded a free flow of cloudy, amber-colored bile. On February 9, the concentration of bilirubin had dropped to 5 mg. in each 100 cc. of serum.

The patient was dismissed from observation on February 11 on a diet high in carbohydrate and low in protein, and calcium lactate in doses of 60 grains (4 Gm.) three times a day was given. On March 3, he reported that the jaundice had disappeared, and that his weight and strength were approaching normal.

CASE 9.—A man, aged 54, registered at the clinic on Dec. 5, 1932, with the complaint of jaundice of forty days' duration. In July, 1932, arthritic pains appeared in the spinal column, knees and elbows, and in September the patient began the use of 3 capsules of oxyliodide three times a day. On September 10, an attack of nausea, vomiting and diarrhea that lasted for twenty-four hours occurred. The oxyliodide was taken over periods of ten days with intervals of the same duration until October 20. On October 10, an infection of the upper portion of the respiratory tract apparently developed. On October 15, an urticarial rash appeared and lasted for two days. On October 23, there was a second attack of nausea and malaise. On October 25, jaundice appeared, and reached its greatest intensity within a few days. A cholecystographic examination at the height of the jaundice showed that the gallbladder was not functioning. The jaundice had been gradually clearing.

General physical examination gave negative results except for the presence of a slight grade of jaundice and a tender liver extending about 5 cm. below the costal margin on deep inspiration.

The bromsulphalein test of hepatic function revealed retention of dye, graded 2. The concentration of bilirubin was 1.6 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Cholecystographic examination revealed that the gallbladder was functioning normally. Our diagnosis was toxic cirrhosis due to oxyliodide and arthritis. The patient was advised to continue the diet high in carbohydrates and to avoid cinchophen or any of its derivatives in the future. The foci of infection will be removed later, and physical therapy is to be continued. The patient was dismissed from observation on December 8.

Comment.—The three patients, cases 7, 8 and 9, presented themselves at the clinic after the stage of recovery had been well established. The course of their illness had been mild, of average duration (from thirty to forty days) and without mental symptoms. The relative mildness of the process in cases 7 and 9 is further attested to by the retention of dye, graded 2, at the end of the phase of jaundice, in contrast to the

64. Comfort, M. W.: Toxic Cirrhosis Due to Derivatives of Cinchophen: Report of Four Nonfatal Cases, Proc. Staff Meet., Mayo Clin. **7**:419 (July 20) 1932.

higher grades of retention which persist in the more severe cases for even two or three months after the disappearance of jaundice. The possibility of obtaining normal cholecystograms in the presence of moderate diffuse hepatic disease is illustrated in cases 7 and 9. In these cases, no treatment other than the use of a diet high in carbohydrates and avoidance of further use of the drug seemed necessary.

Group 5 is composed of severe cases.

Case 10 (previously reported from the clinical standpoint by Comfort).—A man, aged 64, came to the clinic on May 24, 1932, with the complaint of loss of weight and strength together with jaundice. Six weeks before admission he began taking Cass' rheumatism remedy for muscular pains. It was estimated that not more than 55 grains (3.5 Gm.) of cinchophen had been taken. On May 5, the urine was noticed to be darker than usual, and vomiting occurred occasionally. A week later the skin was definitely yellow, and thereafter the degree of jaundice increased rapidly. In the last two weeks before admission the patient had slept most of the time, and had lost 20 pounds (9 Kg.).

The patient was stuporous and very weak, the jaundice was intense, and the liver and spleen could not be palpated. The concentration of bilirubin was 25 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. The patient was placed on a diet high in carbohydrates and low in protein, and was given intravenously 1,000 cc. of a 10 per cent solution of dextrose and 1 per cent sodium chloride daily. On May 26, 27 and 30 and June 1, a large quantity of bile-stained fluid was obtained by duodenal drainage, and after June 4 amber-colored bile was recovered from the duodenum, and the concentration of serum bilirubin fell, at first slowly, then rapidly. The urine contained no lead or arsenic. The galactose tolerance test disclosed 5.1 Gm. of reducing substance in the urine. On June 20, the margin of the liver was barely palpable, and the galactose tolerance test revealed the presence of 2.15 Gm. of reducing substance. The patient's general condition had improved rapidly, and he was dismissed on a diet high in carbohydrates and low in protein, to which were added large quantities of dextrose and bread. The diagnosis was toxic cirrhosis caused by cinchophen poisoning.

On August 31, four months after the onset of jaundice, the condition of the patient was excellent; the liver was still barely palpable, the concentration of bilirubin was 1.2 mg. in each 100 cc. of serum, the van den Bergh reaction was indirect, the retention of dye was graded 2, and the gallbladder was functioning normally, as revealed by cholecystographic examination.

Case 11 (previously reported from the clinical standpoint by Comfort).—A man, aged 46, registered at the clinic on Dec. 29, 1930. One year previously he noticed slight ataxia and paresthesia of the legs, more marked on the left. The condition was partially relieved by the administration of 5 grains (0.3 Gm.) of cinchophen three times a day. The patient had taken a total of about 1,260 grains (82 Gm.) of the drug over a period of three months previous to his registration. Ten days previous to registration he noticed vague epigastric distress and soreness, jaundice, dark urine and clay-colored stools.

On admission the patient was deeply jaundiced, very weak and drowsy. The edge of the liver was palpable about 5 cm. below the right costal margin on deep inspiration, and was tender. The spleen was not palpated. The urine contained a moderate amount of albumin, bile and casts, but no lead or arsenic. The concentration of bilirubin was 15 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. A free flow of amber-colored bile was obtained on

repeated duodenal drainage. From January 1 to 17, the patient was given intravenous injections of from 150 to 500 cc. of 20 per cent solution of dextrose daily. When he was dismissed on January 29, the concentration of bilirubin was 4.3 mg. in each 100 cc. of serum. Weakness was still marked. The results of neurologic examination were indeterminate.

The patient returned for examination on April 8, his chief complaints being persistent weakness, gaseous abdominal distress, constipation and paresthesia of the legs. The liver and spleen were not palpated. The concentration of bilirubin was 2.2 mg. in each 100 cc. of serum, and the van den Bergh reaction was indirect. The bromsulphalein test of hepatic function revealed retention of dye, graded 2. The neurologic changes were essentially the same. By June 9 the patient's strength was much increased. The liver could just be felt at the costal margin. The bromsulphalein test of hepatic function disclosed retention of dye graded 1 and hepatic injury persisting six months after the onset of jaundice. On August 17, his general condition was excellent. The concentration of bilirubin was 1.4 mg. in each 100 cc. of serum, and the van den Bergh reaction was indirect. The retention of dye was graded 0.

Case 12 (previously reported from the clinical standpoint by Comfort).—A man, aged 61, registered at the clinic on March 23, 1932. During the preceding six months, because of arthritis of the hip, he took Renton's rheumatic tablets, in an amount containing approximately 1,050 grains (68 Gm.) of cinchophen. Fourteen days before registration, jaundice, with dark urine and clay-colored stools, but without pain or pruritus, began. The degree of jaundice increased rapidly; the patient lost weight, strength and appetite, and he became slightly drowsy.

On admission, the patient was deeply jaundiced, and the liver was slightly enlarged and tender. A roentgenogram of the right hip disclosed slight thickening along the lower margin of the joint. The concentration of bilirubin was 15 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. On March 26, the concentration of bilirubin reached 17.8 mg. in each 100 cc. of serum. The galactose tolerance test revealed 3 Gm. of reducing substance in the urine. Daily injections of 1,000 cc. of 10 per cent dextrose and 1 per cent sodium lactate were given, and the concentration of serum bilirubin fell consistently. Large quantities of light amber-colored bile were obtained by duodenal drainage. The patient's strength and weight increased, and the liver became smaller. When he was dismissed on April 12, the concentration of bilirubin was 2.8 mg. in each 100 cc. of serum. A diagnosis of toxic cirrhosis secondary to poisoning by cinchophen was made. On April 27, the patient reported that he had almost completely recovered his strength and weight, and the jaundice had disappeared. On July 7, his condition was excellent, and the concentration of bilirubin was 1.5 mg. in each 100 cc. of serum. The van den Bergh reaction was indirect, but the bromsulphalein test of hepatic function revealed retention of dye graded 4. On Oct. 17, 1932, the edge of the liver descended to the costal margin on inspiration, and the concentration of bilirubin was 1 mg. in each 100 cc. of serum. That the function of the liver had not returned to normal after seven months was indicated by retention of bromsulphalein, graded 2.

Case 13.—A woman, aged 60, was examined at the clinic on Aug. 8, 1932. She had had progressive rheumatic pains in the shoulders, arms and wrists from early winter until May, 1932. On May 14, her physician prescribed cinchophen, 5 grains (0.3 Gm.) four times a day, which she took for ten days, with relief from the pain. On May 27, urticaria appeared and persisted for one week. About

July 1 exhaustion, drowsiness and nausea developed, and she lost 10 pounds (4.5 Kg.). On August 1, jaundice was noticed, and on examination a week later this was very intense. There were associated anorexia and soreness in the upper part of the abdomen.

General physical examination revealed that the edge of the liver was easily palpable and soft. The concentration of bilirubin was 50 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct (fig. 1). The urine revealed the presence of bile and tyrosine, but otherwise was normal. The cholesterol content was 228 mg., and the cholesterol esters, 64 mg. in each 100 cc. of blood. Repeated determinations of galactose tolerance gave normal results except on one occasion when 4.22 Gm. of reducing substance appeared in the urine. This occurred during a mild relapse in the clinical condition.

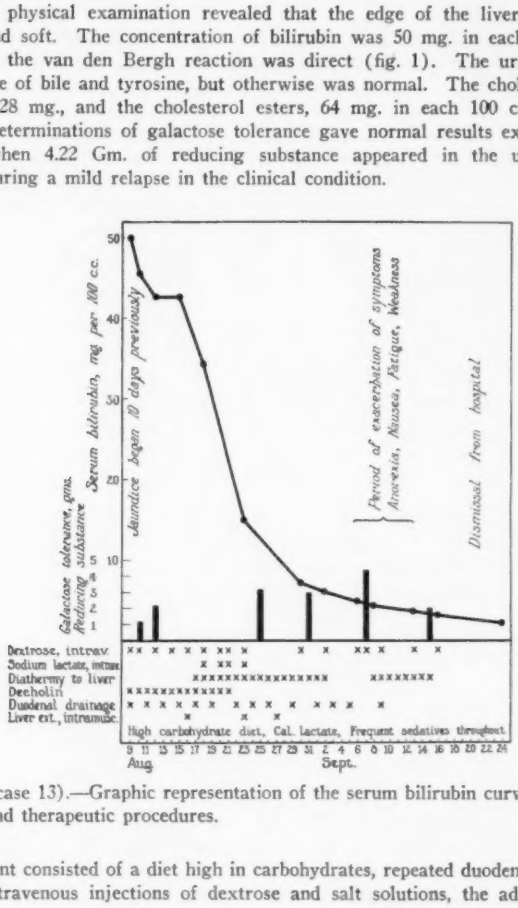

Fig. 1 (case 13).—Graphic representation of the serum bilirubin curve, galactose tolerance and therapeutic procedures.

Treatment consisted of a diet high in carbohydrates, repeated duodenal drainage, repeated intravenous injections of dextrose and salt solutions, the administration of calcium lactate by mouth, occasional intravenous injections of sodium lactate, diathermy over the hepatic region and occasional intramuscular injections of liver extracts. Gradually, clinical improvement resulted, with a coincident decline in the value for serum bilirubin except for a few days when the jaundice was nearly cleared, at which time, nausea, anorexia, weakness and exhaustion recurred. On October 13, the van den Bergh reaction was still direct, and the concentration of bilirubin measured 1.5 mg. in each 100 cc. of serum. The bromsulphalein test of hepatic function revealed retention, graded 2. The details of the laboratory data and treatment given are shown in figure 1. The patient remained under observation until November 1, at which time she felt well and was almost free from jaundice.

CASE 14 (previously reported from the clinical standpoint by Weir [65]).—A man, aged 56, registered at the clinic on Dec. 21, 1926. During the previous year he had suffered from sciatic pains in the right leg, and six weeks before admission his physician prescribed cinchophen. Two weeks afterward jaundice without pain or pruritus appeared, and two weeks later edema of the lower extremities and progressively increasing abdominal enlargement were noticed.

The patient was moderately jaundiced, the abdomen was tensely distended with fluid, and the legs were moderately edematous. The liver and spleen were not palpated. The urine contained bile. The concentration of bilirubin was 8.3 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Diuresis followed the administration of ammonium chloride and merbaphen, and restriction of the intake of fluid and salt resulted in the disappearance of the ascites and edema and loss of 37 pounds (16.8 Kg.) before dismissal. At this time, six weeks after the onset of jaundice, the patient was almost free from jaundice, the concentration of bilirubin being 2.7 mg. in each 100 cc. of serum. In a letter dated Aug. 26, 1928, the patient reported that he was in good condition.

Comment.—In addition to the concentration of serum bilirubin, the mental symptoms, loss of strength and ascites act as reliable indexes of the intensity of the hepatic injury. In cases 10, 11, 12, 13 and 14, one or more of these conditions were present to a degree to warrant classification of the cases as examples of severe toxic cirrhosis. In all 5 cases, the extreme loss of strength and the general debility rendered the prognosis exceedingly grave on admission. The unfavorable prognosis was emphasized in case 10, and especially in case 13, by the depth of the concentration of serum bilirubin; in cases 10, 11 and 12, it was emphasized by the presence of mental symptoms to a degree that justified a fear of impending coma, and in case 14, by the presence of ascites. In case 10, the diet low in carbohydrates and calories imposed before admission had contributed to the seriousness of the patient's condition by causing a diminution in the glycogen reserve of the liver. The rapidity with which this patient responded to diet high in carbohydrates and to intravenous injections of dextrose was startling. Similar experiences with patients denied carbohydrates before admission have served to confirm clinically the experimental evidence of the value of dextrose in the treatment of hepatic injury, and have led us to believe that at least the duration of the disability is shortened and even death averted, as it may have been by such means in the foregoing cases in which jaundice was severe.

The duration of the jaundice was only slightly longer than in the cases in which the severity of the disease was moderate. However, further evidence of the severity of the condition is found in the prolonged period of retention of dye which followed the clearing of jaundice in cases 10, 11, 12 and 13. The retention of dye was graded 2 in

65. Weir, J. F.: The Association of Jaundice and Ascites in Diseases of the Liver, J. A. M. A. **91**:1888 (Dec. 15) 1928.

1 case, and was graded 4 in another at the end of approximately four months. The retention of dye was graded 1 in case 11, five and a half months after the disappearance of jaundice, and was graded 2 in case 12, seven months after the disappearance of jaundice. The malaise and loss of strength usually disappeared within two months after the concentration of bilirubin in the serum approached normal; the patient apparently regained his health long before the functional rehabilitation of the liver was complete as indicated by the bromsulphalein test.

The galactose tolerance test was positive, or questionably so, in the 3 cases in which it was carried out, and served to confirm our clinical impression of diffuse hepatic injury.

The liver was palpable and presumably enlarged in cases 11, 12 and 13 and not palpable in cases 10 and 14. It is our impression that the liver is usually enlarged in nonfatal cases, and at necropsy the liver in the fatal cases, with one exception, was smaller than normal, often markedly diminished in size. The fact that a liver is not palpable in a case in which symptoms and other findings suggest a process of more than ordinary severity should increase the gravity of the prognosis. The opposite is not necessarily true, for a liver may be apparently enlarged and yet be found small at necropsy.

Ascites and jaundice together lend an especially bad prognosis to the case, and relatively few patients with such a combination recover. In the total group of 117 cases, ascites and jaundice were present in 13. The patient in case 14 and only 2 other patients recovered. In the usual case it is well to disregard the ascites and treat the liver energetically with every means at command. When the general condition has improved and the mental and nervous symptoms have disappeared, cautious use of diuretics may be attempted.

Group 6 is composed of fatal cases.

Case 15 (previously reported from the pathologic standpoint by Beaver and Robertson [66]).—A man, aged 37, last registered at the clinic on Aug. 1, 1929. On March 13, 1923, partial thyroidectomy was performed because of exophthalmic goiter. At that time there was no evidence of hepatic injury. On Aug. 1, 1929, he returned to the clinic, stating that for the previous month he had been taking atophan, 3 tablets daily, on the advice of his physician, for chronic infectious arthritis. One week before admission he began to have chills, high fever and painless jaundice, which rapidly deepened and became associated with much weakness and vomiting.

On admission the patient was not mentally clear; he was drowsy, and slept a great deal. His memory was poor for details. The jaundice was moderate. The edge of the liver was not palpable. The concentration of bilirubin was 14.5 mg. in

66. Beaver, D. C., and Robertson, H. E.: The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning: A Review of Five Fatal Cases, Am. J. Path. **7**:237 (May) 1931.

each 100 cc. of serum, and the van den Bergh reaction was direct. Our diagnosis was toxic cirrhosis due to cinchophen. On August 2, the patient became more confused and uncooperative, sleepy and restless. Death occurred on August 4, eleven days after the onset of jaundice. At necropsy the liver weighed 1,320 Gm., and the diagnosis was toxic cirrhosis.

Case 16 (previously reported from the clinical standpoint by Stacy and Vanzant,[67] and from the pathologic standpoint by Beaver and Robertson).—A woman, aged 52, registered at the clinic in December, 1929. In 1922, she received treatment with radium at the clinic for epithelioma of the uterine cervix, from which she afterward had no trouble. In October, 1931, she began to take from 1 to 3 tablets of cinchophen daily for sciatic pain, but discontinued taking the drug after six weeks, when nausea and vomiting appeared. Jaundice without pruritus developed one week later, seven days before admission.

The jaundice was deep and bright orange-yellow. Nausea was the only other complaint. The liver was palpable, and the spleen was slightly enlarged. The concentration of bilirubin was 39 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Bile was not obtained on duodenal drainage or in the stools. Treatment consisted of a diet high in carbohydrates, calcium lactate by mouth and calcium chloride and dextrose intravenously, both with and without insulin. The liver daily became smaller, and drowsiness, stupor and coma developed on the fourth day. Death occurred on the ninth day, sixteen days after the development of jaundice, with terminal hyperpyrexia and bronchopneumonia. At necropsy the liver weighed 904 Gm., and the typical gross and microscopic picture of acute yellow atrophy was noted. There was a recurrence of the malignant process in the pelvis with involvement of the sciatic nerves.

Case 17 (previously reported from the clinical standpoint by Snell and Jordan[63] and Weir and Jordan,[68] and from the pathologic standpoint by Beaver and Robertson[66]).—A deeply jaundiced woman, aged 57, presented herself at the clinic on July 8, 1929. In February, 1929, after she had taken 9 capsules of oxyliodide prescribed by her physician for arthritis; administration of the drug was discontinued because of generalized pruritus. The itching then ceased. In April, 1929, the same symptoms followed the taking of only 1 powder, and the medication was again discontinued. During the latter part of May, 2 tablets of oxyliodide after each meal and at bedtime were prescribed, and the itching reappeared after 2 tablets had been ingested. On the advice of her physician use of the tablets was continued; anorexia and asthenia developed, and she lost from 10 to 15 pounds (4.5 to 6.8 Kg.) After approximately 250 tablets had been taken, their use was discontinued thirteen days before the patient's admission to the clinic, and progressively deepening jaundice developed two days later.

On examination, loss of weight, deep jaundice and arthritis of the hands were noted. The concentration of bilirubin varied from 30.4 to 44.4 mg. in each 100 cc. of serum. Duodenal drainage yielded only small amounts of clear, amber-colored bile. The patient's condition remained stationary until July 22, when nausea, vomiting and subcutaneous hemorrhages developed. An irrational, stuporous state rapidly changed into coma with hyperpyrexia. In spite of vigorous intravenous treatment with dextrose, death occurred on July 26, twenty-nine days after the onset of jaundice.

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67. Stacy, Leda J., and Vanzant, Frances R.: Poisoning from Cinchophen, Minnesota Med. **13**:327 (May) 1930.

68. Weir, J. F., and Jordan, F. M.: Clinical Consideration of Some Types of Intrahepatic Jaundice, M. Clin. North America **13**:1439 (May) 1930.

At necropsy the liver weighed 640 Gm., and presented the typical picture of acute yellow atrophy. Numerous hemorrhages were noted throughout the body.

Case 18 (previously reported from the clinical standpoint by McVicar and Weir,[69] and from the pathologic standpoint by Beaver and Robertson).—A woman, aged 37, registered at the clinic on April 19, 1928. Twelve months previously her first child was born; slight vomiting complicated pregnancy. Since that time she had been exhausted and annoyed by generalized aching, for which she took atophan. Four weeks before admission to the clinic nausea developed; later, itching was noticed, and two weeks before admission jaundice appeared. Epigastric pain was experienced two days before her arrival at the clinic. The concentration of bilirubin was 6 mg. in each 100 cc. of serum, and duodenal drainage revealed satisfactory secretion of bile. The jaundice cleared rapidly, and after a normal cholecystogram had been obtained the patient was dismissed on April 26, 1928.

About June 1, following an attack of nausea and vomiting, the jaundice reappeared, and when the patient was readmitted on July 10 the jaundice was deep. The concentration of bilirubin was 30 mg. in each 100 cc. of serum. Little bile was obtained by duodenal drainage. Prostration, anorexia and nausea were marked. An erythematous eruption, abdominal distention, edema and delirium appeared. Death, with a terminal fall in the concentration of bilirubin to 20 mg. in each 100 cc. of serum, occurred on July 29. At necropsy the liver presented gross and histologic evidence of acute toxic cirrhosis, and weighed 1,045 Gm. There was no evidence of disease in the gallbladder, bile ducts or pancreas.

Case 19 (previously reported from the pathologic standpoint by Beaver and Robertson).—A man, aged 62, registered at the clinic in April, 1930. Five weeks previously there was pain in the left shoulder and the hands, for which he took oxyliodide on the advice of his physician, using 2 boxes of the capsules. His appetite, strength and weight began to fail. Three weeks before admission the urine became dark, and jaundice without pruritus developed.

Brilliant yellow icterus of moderate grade was present. The liver and spleen were not palpated. On April 29, 50 cc. of light amber-colored bile was recovered on duodenal drainage. Until May 8, the concentration of bilirubin was about 10 mg. in each 100 cc. of serum. On May 21, it diminished to 2.9 mg., and the van den Bergh reaction was direct. Our diagnosis was toxic cirrhosis due to cinchophen poisoning, and the patient was dismissed, with instructions that his diet should be high in carbohydrates.

The patient returned to the clinic on August 2, stating that he had improved somewhat after leaving the hospital. His jaundice had never cleared entirely, and he continued to be troubled with insomnia, weakness, anorexia and arthritis. He was moderately icteric. The concentration of bilirubin was 8.8 mg. in each 100 cc. of serum. The liver was definitely enlarged, and extended 2 cm. below the costal margin. On August 6, 50 cc. of light amber-colored bile was obtained by duodenal drainage. On August 12, the concentration of bilirubin reached 16.6 mg. in each 100 cc. of serum, the patient's condition grew worse, and respiration was slow. On August 26, the concentration of urea reached 60 mg. in each 100 cc. of blood, the stupor deepened into coma, and death ensued. At necropsy the liver weighed 1,134 Gm. and presented the picture of toxic cirrhosis. The peritoneal cavity contained 2,000 cc. of fluid.

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69. McVicar, C. S., and Weir, J. F.: Acute Yellow Atrophy, Possibly Due to Poisoning by Atophan, M. Clin. North America **12**:1526 (May) 1929.

Comment.—All of the patients in the fatal group (cases 15, 16, 17, 18 and 19) had used cinchophen or oxyliodide. Cases 15, 16 and 17 were of the fulminating type, and the drug had been used consistently for from one to two months. Weakness, anorexia, nausea and vomiting were the first symptoms, and progressed. Later, nervous features, apathy, drowsiness, delirium and coma developed, ending in death eleven, sixteen and nineteen days, respectively, after the onset of jaundice. The retention of bilirubin in the blood varied from 14.5 to 44.4 mg. In case 17 there was a progressive increase of the serum bilirubin. The liver was palpable in cases 16 and 19; in case 16 it decreased in size with the progress of the disease. It is worthy of note that pruritus was the first symptom in case 17, and that use of the drug was continued on the recommendation of the patient's physician. It is now known that administration of the drug should have been stopped promptly.

In the 2 chronic cases (18 and 19), after the patients apparently had made a preliminary recovery, relapses occurred and were possibly caused by further use of the drug. In case 18, the drug had been used intermittently for more than a year, and the relapse may have been caused by failure of the nodular hyperplasia to compensate fully for the previous chronic injury. Terminal symptoms of portal obstruction in the form of ascites and edema occurred in both of these cases. In case 19, a terminal rise in the serum bilirubin occurred, and in the other (18), a terminal fall.

Intensive treatment in these 5 cases had no effect in staying the fatal outcome. The marked asthenia shortly after the onset of jaundice, the persisting anorexia and nausea, the depth of the jaundice, in cases 15, 16 and 17, and the relapse, in cases 18 and 19, were definitely poor prognostic signs. Some of the patients in the other groups who recovered had jaundice as deep or deeper than that which occurred in the fatal cases, but the other symptoms were not prominent and recovery occurred, although the prognosis at first seemed doubtful.

PATHOLOGIC CHANGES

Necropsy was performed in the 5 fatal cases and in 40 of the 61 fatal cases reported in the literature, and in every case the liver was the organ most severely injured. It presented the picture of acute or subacute atrophy or of toxic cirrhosis. It varied in weight from 450 Gm. in the case of Anderson and Teter to 1,950 Gm. in the case of Reichle. Beaver and Robertson have pointed out that toxic cirrhosis due to cinchophen fulfils the three pathologic characteristics of toxic cirrhosis: (1) relatively rapid necrosis and autolysis of the hepatic parenchyma resulting in atrophy of the liver, (2) a relative increase of connective tissue which arises from parenchymal loss without much proliferative

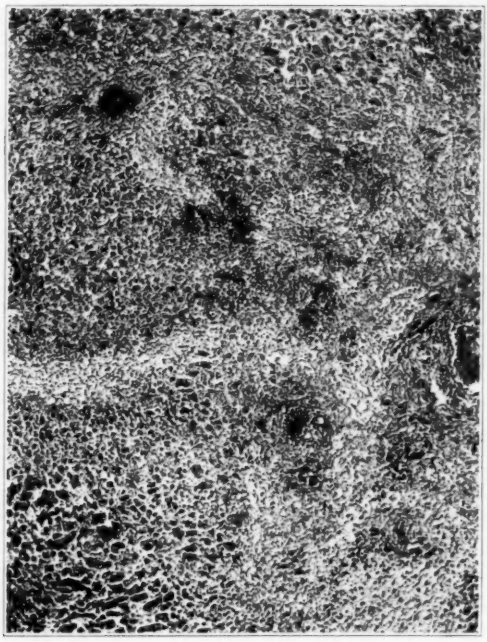

Fig. 2.—Acute stage: Extreme disorganization and necrosis of hepatic cells; congested sinusoids (hematoxylin and eosin; × 65).

Fig. 3.—Subacute stage: Complete dismantling of lobule following necrosis of hepatic cells. The cellular detritus has been cleared. The lobular sinusoids and reticulum are prominently displayed. Some sinusoids and the central vein are congested; other sinusoids with the reticulum are collapsed (hematoxylin and eosin; × 120).

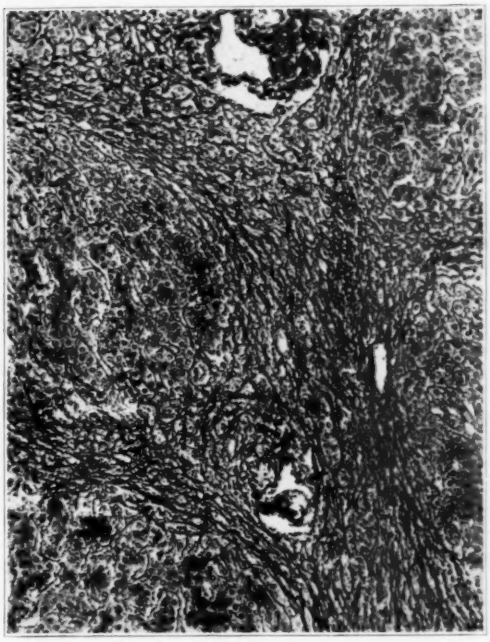

Fig. 4.—Chronic state (early toxic cirrhosis): Compression of skeletonized lobule by growing parenchymal nodules, as revealed by silver impregnation method of Perdrau. A central vein is lying in compressed lobular stroma at the periphery of a regenerated nodule at the right (hematoxylin and eosin; × 110).

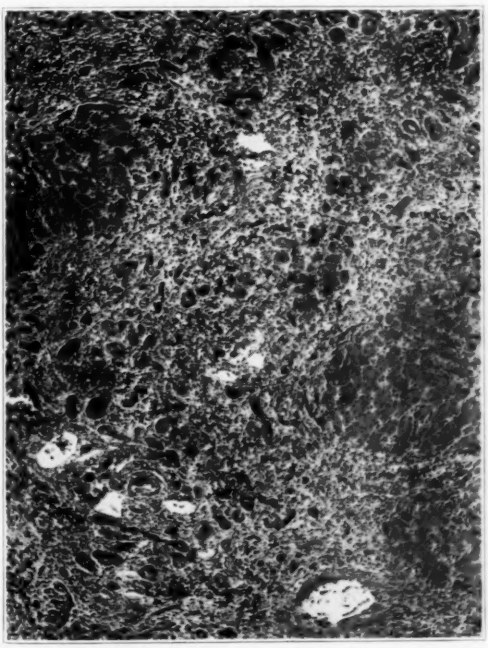

Fig. 5.—Chronic atrophy (early toxic cirrhosis): Nodules of regenerating hepatic cells. The hepatic stroma is shrunken, with sequential narrowing of the sinusoidal bed (hematoxylin and eosin; × 65).

reaction on the part of the connective tissue framework or the vascular apparatus of the liver and (3) regeneration predicted by the duration of life following the initial atrophy, arising as reformed nodules of the hepatic parenchyma from existent parts spared by the initial necrosis. The connective tissue shows somewhat more proliferation. Rabinowitz likewise felt that cirrhosis and nodular hyperplasia would result. Figures 2, 3, 4 and 5 show the various stages in the pathogenesis of the hepatic lesions.

The distinctive character of the pathogenesis in fatal cases has been confirmed by observers other than Beaver and Robertson So far as we know there has been only 1 case in which the liver was examined after recovery from jaundice (our case 4). In that case, the surgeon described the liver as nodular, as of almost normal size and consistence and as presenting a picture of cirrhosis which, as we have pointed out, may be interpreted to mean nodular hyperplasia without an obvious increase in connective tissue—a pathologic process in keeping with our concept of toxic cirrhosis. Whether the regeneration and nodular hyperplasia are present in all nonfatal cases, or whether portal obstruction or hepatic insufficiency eventually will develop, can be settled only by further observation of the patients over a period of years.

GENERAL COMMENT

Although 98 cases of toxic cirrhosis from the use of cinchophen or preparations containing it (exclusive of those previously reported from the Mayo Clinic) have been reported in the literature, this does not represent all such cases. Thus, Rabinowitz stated that Kessel, in a personal communication, reported that he had seen 13 such cases. Bassler [70] stated that he had seen 9 cases, in 2 of which the results were fatal. Similar reports are given in the papers of Reichle and of Lind. Furthermore, there is a group of subclinical cases with definite hepatic injury. Thus, 1 of Ross' patients, 1 of Klinkert's patients and 2 of our patients did not reveal evidences of jaundice, and Cabot's second patient and Lind's patient had little jaundice. Undoubtedly many other cases have escaped detection. It is also possible that many of the other toxic manifestations, such as the cutaneous and anaphylactic features, may be associated with hepatic injury, for we see these symptoms in other types of hepatic disease. In passing, it is worthy of note that we have been unable to find any reports in the French literature.

The amount of the drug used varied in the cases in which the dosage was recorded, from 54 grains (3.6 Gm.) given in five weeks to 7,200 grains (480 Gm.) given in four months. An occasional fatal result

70. Bassler, Anthony: Toxic Hepatitis due to Cinchophen, J. A. M. A. **99**:495 (Aug. 6) 1932.

followed the use of a very small amount of the drug, suggesting initial idiosyncrasy. In other cases, sensitiveness seemed to be acquired, as in de Rezende's first case. The drug was usually used continuously and seldom intermittently, as advised by Graham.

In the majority of cases, the cinchophen or some preparation of it was used for various types of arthritic, myositic or neuritic pains. Headache was an occasional reason. In 6 cases, biloptin was used for visualization of the gallbladder. In one of Dassen's cases, atophanyl was given intravenously for toxic hepatitis due to mercury, resulting in marked aggravation of the jaundice. In 3 cases cited by Weiss, acute necrosis followed the use of icterosan given for advanced jaundice. Nathorf and Willert saw apparently simple icterus turn into acute yellow atrophy

TABLE 1.—*Distribution of Cases According to Ages of Patients and Outcome of Disease*

	Patients in Different Decades of Life								
Outcome of Disease	Age Unknown	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Total
Fatal	5	2	6	5	12	12	16	3	61
Nonfatal	9	..	4	8	8	13	13	..	55
Unknown	..	..	..	1	..	..	..	..	1
Total	14	2	10	14	20	25	29	3	117

TABLE 2.—*Distribution by Sex*

	Cases of Disease with Given Outcome			
Sex	Fatal	Nonfatal	Unknown	Total
Male	21	26	..	47
Female	37	23	1	61
Unknown	3	6	..	9
Total	61	55	1	117

under daily treatment with icterosan. It would appear that the use of atophan in the treatment of jaundice, as advocated by Brugsch, is not as harmless as he believed.

Incidence.—Since the report of the original case in 1922, an increasing number of cases has been recorded each year. We likewise have seen an increasing number of cases. The increase may be due in part to the increasing number of persons using cinchophen, and in part to the increased suspicion of the possibility of the toxicity of cinchophen. In our practice, we suspect every case of intrahepatic jaundice as being a possible case of toxic cirrhosis until the taking of cinchophen is definitely excluded. A carefully taken history and a chemical analysis of drugs when their character was not known have revealed the condition in cases which we would have missed four or five years ago.

The age of 103 patients is known. Table 1 gives the distribution by decades of life for the fatal, nonfatal and total groups. In 74 of

the 103 cases the disease occurred within the fifth, sixth and seventh decades of life, when rheumatic complaints are most frequent, and may not indicate a greater susceptibility among older persons. There were 47 men and 61 women; in 9 cases the sex was not stated (table 2).

Symptoms.—The initial symptoms of toxic effect are most frequently gastro-intestinal, comprising impairment of appetite, nausea and vomiting. Other symptoms are heartburn, belching and diarrhea. Pruritus, urticaria and weakness are symptoms not uncommonly encountered before the onset of jaundice, and should always warn the physician of danger in the further use of cinchophen. The mechanism of pruritus is unknown, but it resembles a similar reaction occasionally seen with hepatic injury following the use of arsphenamine. In many cases in the literature, symptoms premonitory to the jaundice are not mentioned. These symptoms may precede the jaundice by only a few days, or weeks or months may elapse before the jaundice appears.

TABLE 3.—*Incidence of Jaundice and Its Duration*

Outcome of Disease	Patients with Jaundice of Given Duration in Weeks: Number of Weeks: Unknown	1	2	3	4	5	6	7	8	10	12	16	20	24	28	No. of Weeks: Patients Without Jaundice: Unknown	Total Number of Patients
Fatal	10	9	17	4	7	4	2	..	3	..	..	2	1	1	..	1	61
Nonfatal	13	..	4	3	7	2	7	4	7	1	3	1	..	..	1	3	56
Total	23	9	21	7	14	6	9	4	10	1	3	3	1	1	1	4	117

The onset of jaundice is usually painless; however, in some instances pain is present and may be severe, although not of the grade met in biliary colic. Jaundice may be ushered in by an acute attack of nausea, vomiting, sometimes chills, fever or pain and distress in the region of the liver. The jaundice usually reaches its maximal intensity in a few days. A concentration of bilirubin of from 15 to 20 mg. in each 100 cc. of serum is observed in the moderately severe cases, and less than this in the mild cases, whereas in the fatal cases, as well as in the severe nonfatal cases, a concentration of more than 20 mg. is common, and it may attain 50 mg. for each 100 cc.

In the fatal cases, the jaundice usually remains intense until death; however, there may be a terminal fall, or death may ensue only after the disease has become chronic and the values for serum bilirubin have gradually decreased over a period of weeks. In the milder nonfatal cases, the jaundice may gradually fade from the peak. In the more prolonged and severe cases, the depth of the jaundice may remain stationary for from two to three weeks or more before fading begins. The duration in weeks of the fatal and nonfatal cases is given in table 3. The duration of the jaundice is definitely known in 50 of the 61 fatal cases. In these 50 cases, 52 per cent of the patients died within

two weeks of the appearance of jaundice, 74 per cent within four weeks and 86 per cent within six weeks. Only 8 per cent died after eight weeks. Many of the late deaths followed exploration, recurrence of jaundice or portal obstruction. The duration of the jaundice is definitely known in 40 of the 56 nonfatal cases. Recovery occurred within certain definite periods after the onset of jaundice: in 10 per cent of the cases, in two weeks; in 35 per cent, in four weeks; in 57.5 per cent, in six weeks, and in 85 per cent, in eight weeks, whereas in only 15 per cent was the duration longer than eight weeks. It would appear that most of the fatally affected patients die within six weeks, whereas those not so seriously affected recover in from six to eight weeks. The duration of the condition in nonfatal cases approximates that of the usual case of endemic "catarrhal" jaundice for which the patients seek hospitalization.

Anorexia, weakness and dehydration are often prominent features even when the jaundice is mild. Nausea may be troublesome, and pruritus is often distressing. The disappearance of the symptoms usually accompanies diminution in the depth of the jaundice, and signals the end of the hepatolysis and the beginning of recovery. In a few cases, however, the jaundice has been clearing, and weight and strength have been improving when the jaundice has recurred. Recurrences were noted in 4 cases reported in the literature, and in 2 observed by us. A fatal result ensued in 4 of the 6 cases. Some of the deaths were due to the further use of atophan. Temporary improvement should not lead to a feeling of false security and cessation of energetic treatment.

In the moderately severe nonfatal cases, headache, drowsiness and restlessness may awaken the fear that stupor and terminal coma are near. Stupor, coma, delirium and convulsions are the usual precursors of death. Seldom, if ever, does the comatose patient recover. Paralysis associated with pathologic reflexes, the presence or absence of deep reflexes and a peculiar spasticity suggestive of that seen in diseases of the extrapyramidal system and for which no gross or microscopic lesion of the central nervous system exists to explain the clinical picture may be present in the last few days. Terminal hyperpyrexia, anuria, with a rise of the value for urea in the blood, edema, anemia or a fall in the concentration of the serum bilirubin may appear.

Ascites occurred in the first three weeks of illness in only 2 cases (Cabot's case 1 and Rabinowitz' case 3), and after three weeks in 11 cases, of 117. It is usually a later, terminal phenomenon. In only 2 cases has recovery followed the appearance of ascites (Braun's case and our case 14). Paracentesis may be necessary and was reported by Link, and by Parsons and Harding. Edema may be present without

ascites (noted in 7 cases reported in the literature and in 3 of our cases), or with ascites (noted in 6 reported cases and in 3 of our cases).

Gross hemorrhage from the esophageal veins occurred as a terminal phenomenon in the cases of Willcox (case 3 in his report of 1931) and Cabot (case 1), in the fifth and sixth weeks, respectively, and was associated with ascites. Other hemorrhagic tendencies, including epistaxis, bleeding from the gums, petechiae and purpura, have been noted in fatal cases, but also in some cases in which recovery occurred.[71] Marked anemia was reported by Lambert, and by Parsons and Harding (case 4 in their report of 1932). Leukocytosis is occasionally noted.

In our experience, the liver was palpable and presumably enlarged in the nonfatal cases, even in the cases in which jaundice was not present. In the more severe nonfatal cases, such as our case 10, the liver was not palpated, and this was interpreted to mean a more severe degree of hepatic injury and atrophy. In most of the fatal cases, the liver could not be palpated, and at necropsy it was found to be moderately or strikingly atrophic and small. A rapid diminution in the size of an enlarged liver is of serious prognostic significance, and has been reported in several cases.

The spleen may be palpable, but is usually so only in the more prolonged cases. It has been found enlarged, as in the cases of Rabinowitz (case 1, report of 1928), Bogen (case 1) and Berger and Schweid (case 1).

In some cases diseases other than those for which the cinchophen was given were present. Thus, subacute cholecystitis without stones was present in Kingreen's case. The patient recovered after cholecystectomy had been performed. Cholelithiasis was present in Ross' second case, and the patient died following cholecystectomy. A tumor of the pituitary gland, with diabetes insipidus, was present in Hitzenberger's first case. In Singer's case, ulcerative mitral endocarditis caused death, but the jaundice was interpreted as being caused by cinchophen. Mild diabetes mellitus was present in MacGregor's case, and transient glycosuria in Ross' fourth case. In Rabinowitz' second case (report of 1930), hepatic injury and jaundice necessitated therapeutic abortion, following which the patient recovered. In Ross' third case, the patient had a tuberculous hip, operation on which was followed by death in forty-eight hours; necropsy revealed hepatic necrosis.

Various surgical procedures were carried out on other patients. Thus, abdominal exploration for abdominal pain or indefinite masses was carried out in the cases of Rake, Lowenthal, Mackay and Lowe (case 2), Bogen, Berger and Schweid and Rabinowitz (case 7, report of 1930) and the results were fatal in all. Omentopexy and gastroenterostomy were performed in Parsons and Harding's case (report of

71. Fink.[41] Eimer.[52]

1932) with fatal results. A fatal outcome followed tonsillectomy in Rabinowitz' case 5 (report of 1930). From these results it will be seen that these patients present poor surgical risks, and that any surgical procedure should be avoided if possible.

The urine may contain albumin and tyrosine, as well as bile in appreciable quantities. The stools are clay-colored so long as the liver fails to secrete bile freely. When the liver resumes its secretory functions, bile appears freely in the duodenal drainage, the urine becomes lighter, and the stools become pigmented. The lowering of the concentration of cholesterol and cholesterol esters in the serum, as well as the abnormal output of reducing substances in the urine after the ingestion of galactose, gives valuable information regarding the degree of hepatic injury. The bromsulphalein test of hepatic function is of little value during the phase of jaundice, but is of great value in delineating the time of functional recovery of the liver after the jaundice has cleared. In our case 11, eight months had elapsed before the retention of dye disappeared.

Diagnosis.—The fatal cases of toxic cirrhosis caused by cinchophen are indistinguishable from the cases of acute or subacute yellow atrophy resulting from other causes. The nonfatal cases are indistinguishable from the ordinary case of catarrhal jaundice or of any other condition resulting in toxic hepatitis. Jaundice, nonobstructed bile ducts and a direct van den Bergh reaction are essential to the diagnosis of intrahepatic jaundice, whatever the cause. The diagnosis depends on a history of treatment with cinchophen. The physician will fail to elicit such a history in many cases unless every case of intrahepatic jaundice is considered to be, possibly, a case of cinchophen poisoning, and unless most careful questioning of the patient is carried out. Chemical analysis of a medium the nature of which is not known may be necessary. Suspicion that the medicine contains cinchophen, as well as appreciation of the nature of the symptoms preceding the development of jaundice, may lead to recognition of cases of toxic cirrhosis without jaundice, as in the cases of Klinkert, and in our cases 1 and 2.

Undoubtedly, some cases of idiopathic and catarrhal jaundice will, because of coincidental treatment with cinchophen, be classified as cases of toxic cirrhosis due to cinchophen. It would be much better to accuse the drug falsely than to refuse to recognize the relationship between toxic cirrhosis and cinchophen, and to permit a sensitive patient to take the drug, with recurrence of the acute process and perhaps death, as occurred in the first case reported by Reichle. The diagnosis of toxic cirrhosis due to cinchophen is unusually important because of the serious prognosis as contrasted to that of the usual case of catarrhal jaundice, and because in the nonfatal cases the patient must be pro-

tected and warned against further use of the drug. A correct diagnostic differentiation from diseases of the gallbladder or bile ducts or from portal cirrhosis is obviously important to prevent unnecessary surgical risks and postoperative deaths.

Prognosis.—In view of the high mortality (51 per cent) in the cases reported, the prognosis in all cases should be considered serious until the extent of the hepatic injury can be estimated. Persistent deep jaundice, a decrease in the size of the liver, mental symptoms, ascites and hemorrhagic tendencies are of particularly bad prognostic significance. The prognosis should be guarded even after recovery has set in, for there may be a recurrence. Complete clinical recovery has so far occurred in all nonfatal cases, but not enough time has elapsed since the first cases were seen for one to judge of late results. Years hence, in some of these cases, symptoms of portal obstruction, such as ascites or hemorrhage, may occur, or jaundice may again develop, leading to a fatal issue. This is, at least, to be suspected in the more severe cases.

Treatment.—Treatment is twofold: prophylactic and curative. Cinchophen should be administered only with due recognition of the danger to the occasional patient who may have an idiosyncrasy for the drug. It should not be given to patients who are malnourished or who have hepatic disease. The drug should be prescribed only by a physician. The use of cinchophen in patent remedies and its sale by druggists without a physician's order should be prohibited by law.

When cinchophen is to be used, it should be given intermittently. A full diet rich in carbohydrates should be a part of the treatment with cinchophen. Administration of the drug should be stopped at the first signs of toxicity, such as anorexia, nausea, weakness, vomiting, malaise, pruritus or urticaria, and treatment of the complication should be energetically pushed even before the appearance of jaundice. After the appearance of jaundice, a diet rich in carbohydrates, together with fluids, dextrose and sodium lactate intravenously, calcium lactate by mouth and duodenal drainage, has proved of value in our hands. Dextrose in the hands of some has proved more efficacious when supplemented with insulin. The use of liver extract has been advocated by Bassler, and diathermy is said to be of value.

SUMMARY

Although cinchophen occupies a warranted position in therapeutics, great caution is necessary in its use, as proved by the not infrequent occurrence of toxic manifestations (cutaneous, anaphylactoid, gastrointestinal, cardiac, renal or hepatic). Of these toxic manifestations, the symptoms of toxic cirrhosis are most frequently reported. Since

1923, 19 cases of toxic cirrhosis have been seen in the Mayo Clinic, and 98 cases have been recorded by various authors, 117 in all. Sixty-one of the 117 patients died. Many of the others were seriously ill, and were disabled for from one to three months. The frequency and severity of hepatic involvement establish this as the most important of the toxic manifestations.

Moreover, the frequency of the cases reported in the literature and encountered in our practice is increasing from year to year, and the 117 cases are not all the cases which have occurred. Thus, in the discussion of various cases, physicians have mentioned other unreported cases. The reports of most of the cases have come from the larger medical centers. It would be as unreasonable to assume that toxic cirrhosis caused by cinchophen occurs only in localities where larger medical centers are situated, as it would be reasonable to assume that many cases are undiagnosed or not reported. There is reason to believe that many nonfatal cases are considered to be cases of catarrhal jaundice because of lack of acquaintance with the causal relationship between cinchophen and toxic cirrhosis, with a consequent failure to seek out this cause of intrahepatic jaundice. That toxic cirrhosis without jaundice occurs and that other toxic manifestations precede, and may even accompany, hepatic injury not manifested by jaundice are even less appreciated. If all cases were recognized and reported, the number would be greater, and the problem of toxicity of cinchophen would receive greater attention.

The drug is available in a large variety of preparations; Hench has listed more than thirty. Manufacturers, recognizing the toxicity of the drug, are constantly adding new preparations, some of which are claimed to be nontoxic. It is true that toxic cirrhosis has not been reported as occurring after the use of some of these, but some preparations have so recently been placed on the market that experience with them is insufficient to allow of decision as to their toxicity. Moreover, the total quantity of cinchophen in each preparation is not known. So far, we do not feel justified in assuming that any one preparation is nontoxic.

The universal presence of the quinoline radical in all preparations points suggestively to this as the offending part of the compound. The dosage is relatively unimportant. Toxic symptoms have appeared after doses of all sizes, ranging from 54 grains (3.6 Gm.) given in five weeks to 7,200 grains (480 Gm.) given in four months. An occasional fatal case has followed the use of a very small quantity of the drug, which suggests that an idiosyncrasy was present initially, whereas in other cases the idiosyncrasy seemed to be acquired. Various theories have been evolved to explain the toxicity of the drug, but at present no satisfactory explanation exists, and experimental work has not assisted in solving the problem.

The drug has been used in a variety of conditions, chief of which are the rheumatic disorders, which are of such frequent occurrence in the later decades of life. Use of the drug has been widespread, as the drug has been readily available. Unfortunately, its use and availability have not been under the control of the medical profession. Furthermore, it has been given by some members of the medical profession without adequate knowledge of the dangers attending its use or of the significance of the premonitory symptoms. Thus, in our case 17, continuation of the administration of the drug was advised after the development of pruritus. Nor have all members of the medical profession an adequate appreciation of the seriousness of the injury caused by cinchophen, the mortality rate of which is 51 per cent, or of the risk of surgical procedures in the presence of the injury, as shown by the frequency with which the operation played a part in many of the fatalities. In view of these dangers in the use of cinchophen or allied compounds, the public should be protected by legislation or education. Members of the medical profession should be cognizant not only of the possibilities of toxic symptoms, but also of the early and mild evidences of toxicity, so that the drug may be used cautiously, its administration stopped at the first signs of poisoning, and treatment instituted even before jaundice develops.

STUDIES ON DIGITALIS IN AMBULATORY PATIENTS WITH CARDIAC DISEASE

V. FURTHER OBSERVATIONS ON THE NATURE OF THE CUMULATION OF DIGITALIS

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A study of the elimination of digitalis in man was published in 1929 by Gold and DeGraff.[1] The subjects were ambulatory patients with auricular fibrillation and moderate congestive heart failure. Slowing of the ventricular rate (depression of the auriculoventricular conduction) and the relief of the circulatory failure served as the criteria of the action of digitalis. It was found that during the first few weeks a fixed daily dose of digitalis produced progressive slowing of the ventricular rate, but that after this period the rate remained constant, although the same daily dose was continued without interruption for many weeks. A typical record obtained in the study is reproduced in chart 1. The facts were interpreted in the following manner: The progressive slowing of the ventricular rate in the first period was understood to indicate that the patient was not excreting completely each daily dose of 3 grains (0.2 Gm.), the result being cumulation of the drug, which produced a progressive increase in the intensity of the effects of the digitalis; in the second period the rate of elimination increased, the excretion keeping pace with the daily intake of 3 grains so that no further cumulation could take place. The result was that the ventricular rate reached a level at which it remained.

These explanations appeared to be the most reasonable, although the facts then available did not entirely exclude other possibilities. Since the patients being studied had auricular fibrillation and congestive failure, it seemed possible that the incomplete elimination in the early period of treatment might be due to the heart failure, and that the more

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1. Gold, H., and DeGraff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients: II. The Elimination of Digitalis in Man, J. Clin. Investigation **6**:613 (Feb.) 1929.

complete excretion which occurred later might be ascribed to the greater capacity for elimination resulting from the improved circulation. On the other hand, it also appeared possible that the elimination of the digitalis might have remained constant throughout, the progressive slowing of the heart rate in the early period not being an indication of cumulation of the drug, but a process secondary to the improved cardiac function resulting from the continued use of a small dose of digitalis, a phenomenon which has been termed by other writers the "tonic" action of digitalis.

The general hypothesis advanced in the previous study was that patients do not excrete a fixed quantity of digitalis daily but one that varies with the amount present in the body. It would not be valid if it grew out of special conditions that apply only to patients with auricular fibrillation and congestive heart failure. The present study was planned, therefore, to ascertain the curve of the cumulation of digitalis in patients with a regular sinus rhythm without heart failure, the criteria being changes in the P R interval and in the T wave which may under these conditions be ascribed only to a direct action of the drug and which cannot be considered as indirect effects of an improved state of the general circulation.

METHOD

Observations were started on a series of ambulatory patients attending the clinic for cardiac diseases. Their ages ranged from 6 to 40 years. As already stated, they had regular sinus rhythms and did not present signs of congestive failure. In six, the physical signs were not sufficient to justify a diagnosis of organic heart disease (class E). The remaining patients had organic heart disease, classified etiologically as congenital, rheumatic or unknown.

A uniform specimen of digitalis was employed in the form of the compressed tablets of the dried leaf, supplied by the Heart Committee and standardized by the cat method, 100 mg. (about 1½ grains [about 0.1 Gm.]) constituting 1 cat unit. The drug was dispensed in the clinic, and the daily amount was ordered to be taken in a single dose before retiring.

In order to establish the normal variations in the P R intervals and in the T waves and R T segments (R T—T), several electrocardiograms to be used as controls were usually taken at intervals of a week or longer before the administration of digitalis was started, and in order to ascertain whether or not the effects observed later might have been produced by the first dose alone, the first tracing made during the administration of the drug was frequently taken from twelve to twenty-four hours after the first dose. It was found, however, that the single dose rarely produced changes; hence, in many cases the first electrocardiogram during the use of the drug was not taken until a week or more afterward. During the entire period of observations for total periods up to a year or longer, subsequent tracings were taken at intervals of from one to six weeks.

As has already been mentioned, the changes in the P R intervals and in the R T—T segments were used as criteria of the action of digitalis. The changes were read from the same lead throughout the entire experiment in any given subject, lead I or II being used depending on which was most clearly defined and could

be read with greatest precision. The standardization was recorded on each tracing. The figures for the P R intervals were not identical in different leads, and we have observed differences as high as 0.04 second. The differences, however, remained fairly constant in records taken at different times and presented no difficulty as long as readings were always made from the same lead.

In determining the degrees of change in the R T intervals and the T waves, we did not confine ourselves to the usual procedure of measuring the height of the deflections in millimeters because frequently a change in the form of the R T—T segments quite apparent to the eye was not adequately revealed in such a measurement. We found that it was more practical to compare the changes by matching the tracings according to the form of the R T—T segments or according to the actual height of the T wave in millimeters when that was possible, or according to both, and in this way we succeeded in most instances in dividing the entire series of electrocardiograms belonging to any one patient into groups according to the degree of the change. We then assigned an arbitrary value to each degree of change (each group of tracings) for purposes of charting the intensity of the effects of digitalis during different periods. The study presented an opportunity of comparing a number of electrocardiograms taken for control purposes at vary-

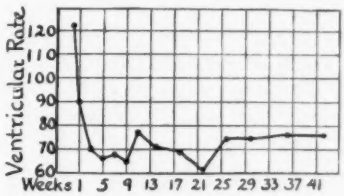

Chart 1.—The changes in the ventricular rate during the continuous administration of a daily dose of 3 grains of digitalis. The patient, E. Q., aged 25, weighed 154 pounds (70 Kg.). The diagnosis was rheumatic heart disease, mitral stenosis and insufficiency, enlargement of the heart and auricular fibrillation (class II A). When this record was started, digitalis had not been administered for three weeks.

ing intervals during periods of six months or longer. The results show that in many instances the T wave and the R T segments remain extraordinarily constant, while in others the form and the height of the T wave show similarly striking variations from time to time without any assignable reason. This is an important source of error that has not been excluded in some electrocardiographic studies found in the literature in which only one or two control records have been taken and in which a change in a patient's clinical condition or the use of some drug is assigned as the cause of the changes in the shape or the height of the T waves—changes that come well within the range of the variations that occurred spontaneously in some of our subjects.

RESULTS

Many difficulties were encountered in the course of the experiments. It was necessary for the subjects to take a daily dose of digitalis without an interruption, or at most only an occasional one, for periods of months, and in many cases it was impossible to sustain the patient's cooperation,

especially as there were no subjective symptoms that required relief or could be relieved by digitalis. Although the subjects were urged and encouraged in every way to report all omissions of daily doses, doubt as to the accuracy of the reports in many cases made it necessary to discontinue the experiment. Intercurrent infections, intestinal upsets, vacations and inclement weather on days of sessions at the clinic (the sessions being held only once a week) often resulted in interruptions in the use of the drug for a week or more, thereby rendering valueless series of observations and tracings made during previous periods which in some cases were of several months' duration. Some patients failed to show any changes in the P R intervals or the R T—T segments of the electrocardiogram, and when changes did not appear even after many weeks or months with doses of as much as 6 grains (0.38 Gm.) daily, the experiments were discontinued. Finally, we may refer to a danger that at all times threatened to vitiate, and in some cases did vitiate, a series of observations in the large numbers of patients with rheumatic heart disease in our group, namely, periods of active carditis. The danger of this factor was particularly striking in the situation presented by two of the children with rheumatic heart disease. In one of these, after three weeks of digitalization with a daily dose of 3 grains, marked changes in the T waves and the P R intervals in lead II (an increase of from 0.15 to 0.26 second) appeared for the first time simultaneously with slight fever and pains in the joints. As the use of the drug was continued, however, the electrocardiographic changes gradually disappeared, and subsequently daily doses up to 9 grains (0.6 Gm.) failed to produce an effect on the P R intervals. In the second case, after six normal and fairly uniform control tracings were made within a period of three months, the next tracing, made on the day on which the use of digitalis was to be started, showed an inverted T wave and a prolonged P R interval. These changes progressed and then subsided spontaneously. They were proved to be due to an attack of rheumatic activity. Since there was no way of ascertaining the proper dose in every case in advance, there were many instances in which failures were recorded because the daily dose was too small to produce an appreciable effect even after months, and other instances in which the dose was so large that toxic symptoms were induced shortly after its administration was begun.

All the foregoing factors contributed their share in reducing the number of successful experiments to such an extent that on only twleve of the seventy-five subjects with whom the study was started was it possible to carry out observations that were adequate for the purpose of the investigation. The essential data obtained in these twelve patients have been summarized in the table.

Patient	Age	Weight, Pounds	Diagnosis*	Duration of Observation, Weeks†	Daily Dose, Grains	Criteria of Action of Digitalis	Effect After First Period‡	Level of Effect After Continued Administration	Duration of Level, Weeks	Effect of Larger Doses§	Size of Larger Doses, Grains
M. C.	11	86	Rheum., E. H., M. S., M. I., RSR, I	75	3	P R (0.15) R T—T, II	± 1+	0.24 4+	16 16	0.32 6+	4½ 4½
L. R.	17	180	Rheum., E. H., M. S., M. I., A. I., RSR, I	84	3	R T—T, II	0	3+	13	6+	4½
A. D.	13	80	Unknown, E. H., M. S., M. I., RSR, I	41	4½	R T—T, II	0	3+	6	5+	6
A. R.	33	132	Rheum., E. H., M. S., M. I., A. S., A. I., RSR, IIa	75	4½	P R (0.18) R T—T, II	0.20 1+	0.22 2+	15 15		
G. W.	13	120	Rheum., E. H., M. S., M. I., RSR, I	35	3	P R (0.16) R T—T, II	0.18 2+	0.22 3+	26 26	0.28 6+	6 6
M. S.	15	110	Rheum., E. H., M. S., M. I., A. S., A. I., RSR, IIa	87	3	P R (0.20) R T—T, II	0.22 1+	0.28 5+	15 23	0.37 8+	4½ 4½
A. S.	16	113	Rheum., E. H., M. S., M. I., RSR, I	39	3	R T—T, II	0	3+	9	5+	4½
E. B.	33	150	E	58	4½ 6	R T—T, II P R (0.20)	1+ 0	4+ 0.28	30 8	6+	6
H. C.	11	60	Cong., E. H., I	50	3 4½	R T—T, II R T—T, II P R, II (0.16)	0 0 0.18	4+ 6+ 0.32	8 11 11	6+	4½
G. V.	8	55	E	45	3	R T—T, II	0	4+	36		
N. H.	29	127	Diabetes, E	56	4½	R T—T, II	0	6+	44		
H. J.	31	115	Rheum., E. H., M. S., M. I., RSR, IIa	48	4½	R T—T, II	0	6+	5#	6+	6

* The diagnoses follow the nomenclature in the "Criteria for the Classification and Diagnosis of Heart Disease;" Rheum., rheumatic; Cong., congenital; E. H., enlargement of the heart; M. S., mitral stenosis; M. I., mitral insufficiency; RSR, regular sinus rhythm; I, IIa, functional classification; A. S., aortic stenosis and A. I., aortic insufficiency; E, possible heart disease.

† This includes the period of control as well as the period after the long period of digitalization during which the drug was withheld for the study of the duration of the action.

‡ Under this heading are included the earliest changes observed after the drug was started. In some cases the heading refers to changes noted twenty-four hours after the first one or two doses; in others, changes noted after the drug was administered for a week or longer. The intensity of the change in the R T—T segment is indicated by +, hence, for example, 5+ is a much greater change than is 1+. The changes in the P R intervals are indicated by the actual readings in seconds taken from the tracings.

§ In cases in which the "larger doses" were not given, it was considered that the absence of gastro-intestinal or any other symptoms of the increased action of digitalis was sufficient to indicate that no appreciable cumulation was taking place during the long period marked "duration of level."

In this case the dose of 4½ grains (0.3 Gm.) produced a marked change in the R T—T segment, which showed no greater change during the succeeding period in which 6 grains was administered daily for twenty-two weeks. The absence of appreciable cumulation is again indicated in this case by the absence of gastro-intestinal symptoms.

With the proper doses it was possible to demonstrate the following facts:

1. One daily dose of digitalis was insufficient to produce the full effects seen after the continued administration of the drug.

2. With the continued daily administration of digitalis a curve of increasing intensity of effects resulted.

3. After a time a level was reached beyond which the effects did not increase in intensity.

4. This level was maintained for a length of time sufficient to insure that the dose could not produce greater effects, by any criterion of the action of digitalis.

5. A larger dose was capable of producing greater effects, which indicated that the criteria employed were sufficiently sensitive to reveal the presence of more digitalis.

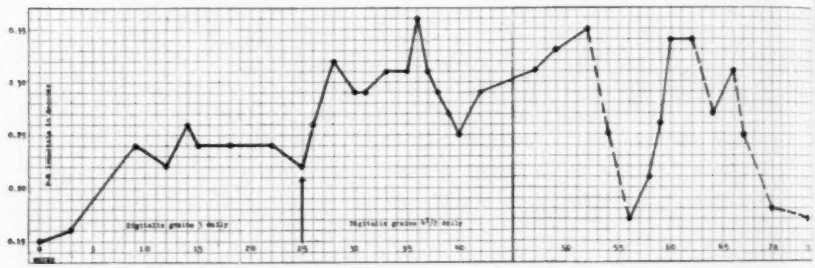

Chart 2.—The changes in the P R intervals during the continuous administration of digitalis. The arrow indicates the point at which the dose was increased from 3 to 4½ grains daily. The broken lines indicate the periods during which the drug was discontinued. The patient, M. C., aged 11 years, had rheumatic heart disease with enlargement of the heart, mitral stenosis and insufficiency and normal sinus rhythm (class I). There were no signs of rheumatic activity.

The details of the records of a few of the subjects have been charted and will serve to illustrate the general type of result obtained in all the others.

The observations in chart 2 were carried out in a patient, aged 11 years, over a continuous period of seventy-five weeks. For the first twenty-five weeks the patient received a daily dose of 3 grains without interruption. In the subsequent twenty-seven weeks the patient received in a similar manner a daily dose of 4½ grains (0.29 Gm.). An examination of this chart shows that the daily dose of 3 grains during the first period of three weeks produced practically no prolongation of the control P R interval (lead I) of 0.15 second. After this daily dose was given for a period of nine weeks the P R interval

slowly increased to 0.24 second. It remained at approximately this level during the subsequent period of sixteen weeks during which the same daily dose was taken. Since practically no effect was produced by the daily dose of 3 grains which was administered during the first three weeks, it is clear that the effects subsequently seen could not be produced by only one dose. That a marked change was evident after the dose was continued for nine weeks showed that cumulation had taken place, and that the latter change did not appreciably increase in intensity, although the same dose was continued for an additional period of nearly four months, showed that during the latter period the excretion was equal to the daily intake, and that cumulation had ceased. In order to ascertain whether further cumulation would have been revealed in the length of the P R interval had it occurred during this period, the dose was increased to 4½ grains daily, with the result that

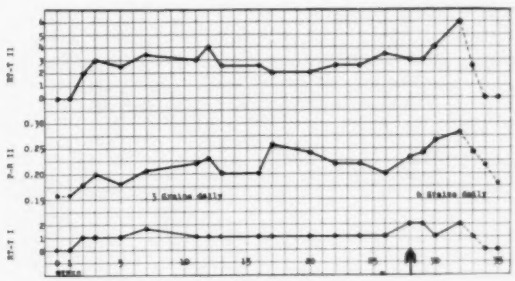

Chart 3.—The changes in the R T intervals and the T waves in leads I and II and in the P R intervals in lead II during the continuous administration of digitalis. The patient, G. W., aged 13 years, had rheumatic heart disease, enlargement of the heart, mitral stenosis and insufficiency and regular sinus rhythm (class I). The arrow indicates the day on which the daily dose of 6 grains was started. The broken lines indicate the period during which the drug was discontinued. In the case of the R T—T segment the numbers are arbitrary values assigned to indicate the intensity of the change.

the P R interval reached a much higher level (0.32 second), at which it remained with wide variations during the subsequent period of about six months during which this daily dose was continued. There were no gastro-intestinal or other symptoms during the entire period to indicate toxicity ascribable to any of the other actions of digitalis. That the effects on auriculoventricular conduction, which in this patient were ascribed to digitalis, were not due to the accident of rheumatic activity, which sometimes gives no other indication of itself than that registered in the electrocardiogram, was seen when the drug was discontinued. The result was a gradual shortening of the P R interval to practically the normal level by the fourth week. The readministration of the drug

produced essentially the same effect as before, and its withdrawal a second time again resulted in a return of the P R interval to the normal level.

The observations in chart 3 were carried out on a patient, aged 13 years, over a continuous period of thirty-five weeks. During the first period of twenty-eight weeks, a daily dose of 3 grains was taken con-

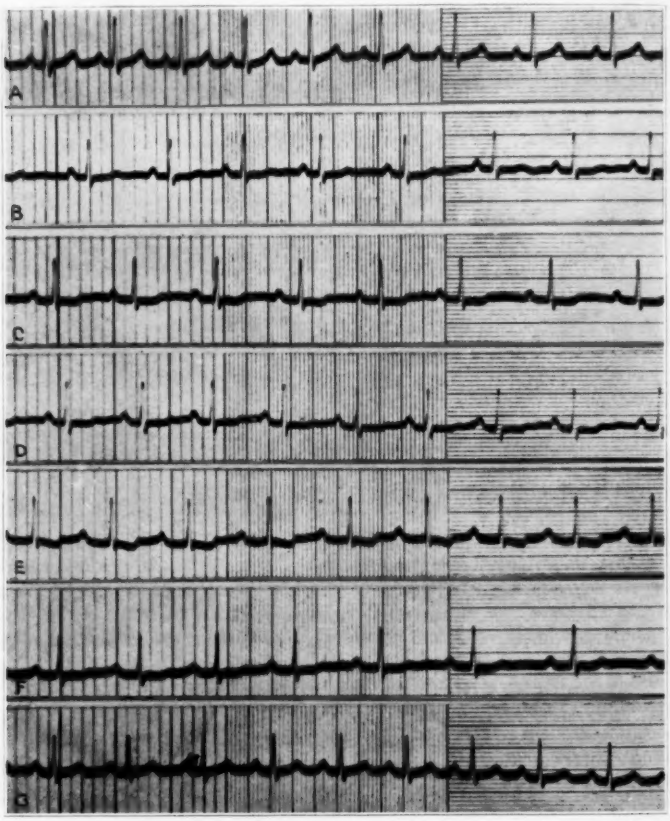

Chart 4.—Seven electrocardiograms (lead II) selected from the total series of twenty-two, which show the types of changes in R T—T to which arbitrary values have been assigned in chart 3. *A* is the control; *B*, the change after 3 grains a day had been given for one week; *C*, the slightly greater change after 3 grains a day had been given for six weeks; *D*, about the same change as in *C*, after 3 grains a day had been given for twenty-six weeks; *E*, the greater change, after 6 grains a day had been given for four weeks; *F*, partial recovery after digitalis was discontinued for one week; *G*, the change after digitalis was discontinued for three weeks.

tinuously. During the subsequent period of four weeks, a daily dose of 6 grains was taken continuously. The dose of 6 grains was not continued long enough to ascertain whether a level of effect would be obtained, the experiment being discontinued when the patient left for the country during the summer. The results obtained with the smaller dose, however, were adequate for our purpose. In this case the changes in the R T—T segement in lead II revealed the phenomenon of cumulation in the greatest detail. An essentially similar curve was obtained with the P R interval in lead II. As seen in the chart, the R T—T interval in lead I was much more resistant to changes by digitalis. Both the R T—T and the P R intervals of lead II showed during the daily dosage of 3 grains progressive increase in the intensity of the effect of digitalis, which reached a level after two weeks, remaining at that level during the subsequent period of twenty-six weeks during which the same daily dosage was given. That a greater effect on the electrocardiogram was

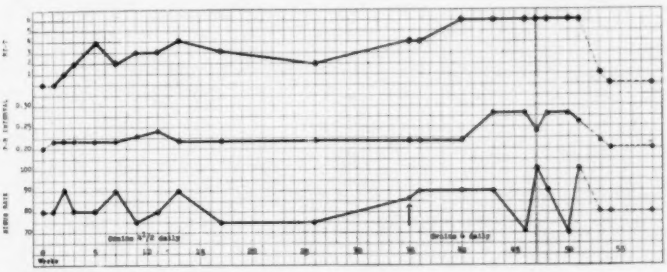

Chart 5.—The changes in the R T—T and the P R intervals and in the sinus rate during the continuous administration of digitalis. These records are taken from lead II only. The patient, E. B., aged 33, was in class E. The arrow indicates the day on which a dosage of 6 grains was started. The broken lines indicate the periods during which the drug was omitted or discontinued.

possible in this case was seen when the dose was increased to 6 grains daily.

In chart 4 are reproduced seven electrocardiograms (lead II) selected from the total of twenty-two taken during the course of the observations on this subject. They serve to show the crucial points in the study and to indicate the character of the changes to which the values in the chart are assigned.

The observations in chart 5 were carried out on a patient, aged 33, over a continuous period of fifty-eight weeks. Six selected tracings (lead II) of the total of twenty-eight made of this subject are reproduced in chart 6. During the first period of thirty-four weeks the patient received a dose of 4½ grains of digitalis daily,[2] and during the

2. In the twenty-sixth week five doses were omitted because the patient failed to return in time to obtain an adequate supply.

subsequent period of sixteen weeks she received a dose of 6 grains daily. The chart records the changes in the R T—T segment, the P R interval and the sinus rate. The curve of cumulation was studied by means of the changes in the R T—T segment, because with these progressive increase in intensity of the action of digitalis in this patient could be followed in greater detail and more satisfactorily than with any other criteria. An examination of the chart shows that after a daily dose of 4½

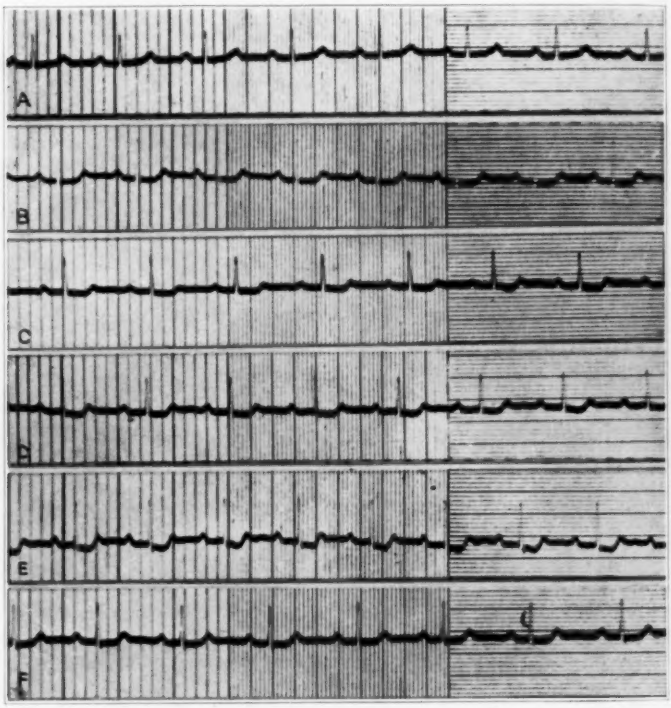

Chart 6.—Six electrocardiograms (lead II) selected from the total series of twenty-eight, which show the types of changes in R T—T to which arbitrary values have been assigned in chart 5: *A* is the control; *B*, the change after 4½ grains a day had been given for one week; *C*, the slightly greater change after 4½ grains a day for five weeks; *D*, about the same change as that in *C*, after 4½ grains a day for thirty-five weeks; *E*, the change after 6 grains a day; *F*, after digitalis was discontinued for two weeks.

grains for one week, there was a slight effect, i. e., lowering of the T wave, and that this change increased in intensity during the subsequent four weeks during which the same daily dose was given. Then the T wave reached a level at which it remained with variations during the sub-

sequent period of twenty-nine weeks in which this daily dose was taken. An increase in the dose to 6 grains daily resulted in a considerable increase in the intensity of the change, showing that the level during the dosage of 4½ grains was due to the fact that no further cumulation was taking place rather than to the failure of the index to reveal further cumulation.

The sinus rate showed marked variations throughout the course of the experiment (rates taken from the electrocardiograms), and the variations showed no relationship to the intensity of the action of digitalis. In this patient the auriculoventricular conduction showed relatively greater resistance to digitalis than did the T wave. Whereas changes in the T wave began to appear fairly promptly after the daily doses of 4½ grains were started, and whereas they continued to show

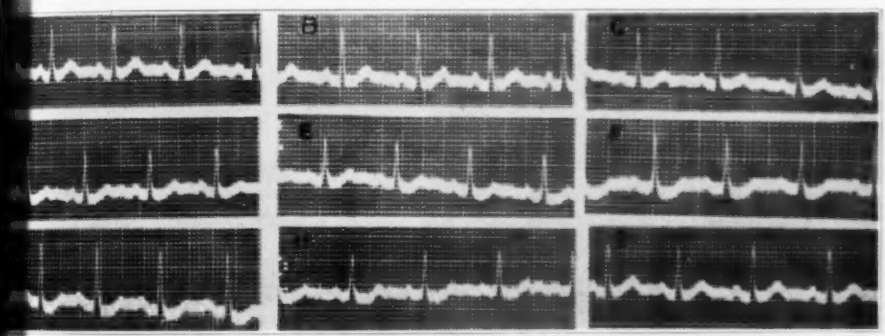

Chart 7.—Nine electrocardiograms (lead II) selected from the total of eighteen taken of patient N. H.: *A*, before digitalis was taken; *B*, no appreciable change twenty-four hours after the first dose of 4½ grains; *C*, slight lowering of the T wave twenty-four hours after the second dose of 4½ grains; *D*, a more marked change in the R T—T interval after 4½ grains a day had been given for one week; *E*, after 4½ grains a day for two weeks; *F*, after 4½ grains (0.3 Gm.) a day for nineteen weeks; *G*, no change greater than that in *F*, after 4½ grains (0.3 Gm.) a day for forty-six weeks; *H*, after digitalis was discontinued for one week; *I*, after digitalis was discontinued for two weeks.

progressive cumulation during a period of four weeks, the P R interval showed no change during this level of the action of digitalis. Marked disturbances in conduction began to appear only after the dosage of 6 grains was started. After this dosage had been continued for three weeks, loss of appetite, mild visual disturbances and depression appeared, which remained throughout the entire period in which this dosage was used, or thirteen weeks after the first appearance of these symptoms. Although marked impairment of the appetite appeared after three weeks, sufficient cumulation did not occur by the end of

thirteen additional weeks of this dosage to induce vomiting. It appears, therefore, that with the daily doses of 4½ grains the cumulation ceased at what might be considered a therapeutic level, whereas with the daily doses of 6 grains in this patient cumulation appears to have ceased at a minor toxic level.

In all of our experiments, when in terms of one of the criteria of the action of digitalis it appeared that cumulation had reached a level and was not increasing, an examination was made of the other effects of digitalis (other electrocardiographic changes and gastro-intestinal symptoms) to ascertain whether these might not indicate that cumulation was still taking place. The record of this patient, as well as that of the previous one, shows the need of taking into consideration more than one effect of digitalis in determining the factor of cumulation. The daily dose of 6 grains produced no prolongation of the P R interval for as long a period as five weeks, which if taken by itself would indicate that no appreciable cumulation had occurred during that time. On the other hand, the T wave showed a considerable increase in the intensity of the effect of digitalis, which would indicate that cumulation had occurred during that period.

In chart 7 are reproduced nine of a series of eighteen tracings which show in greater detail the first portion of the curve of cumulation. These were obtained in a diabetic subject (N. H.), aged 29, with a systolic murmur at the apex but no evidence of organic heart disease. As may be seen from the tracings, neither the first nor the second daily dose of 4½ grains produced any appreciable change in the R T—T segment. A moderate change appeared at the end of the first week, and by the end of the second week a form was established which, with moderate variations from time to time, showed no appreciable increase in the intensity of the action of digitalis, although the same daily dose was continued for a period of forty-six weeks. The absence of gastro-intestinal or any other symptoms referable to the action of digitalis indicated that after the initial period of cumulation, as shown by the R T—T changes, no further cumulation took place.

COMMENT

The experiments carried out in our study, therefore, confirm the conclusions of Gold and DeGraff [1] that patients do not excrete a fixed quantity of digitalis daily but one that varies with the amount present in the body. This is in harmony with the results of experiments with animals performed in 1912 by Hatcher [3] and in 1923 by Gold.[4] Suggestive observations in man also supporting such a view were published

3. Hatcher, R. A.: The Persistence of Action of the Digitalins, Arch. Int. Med. **10**:268 (Sept.) 1912.

4. Gold, H.: Digitalis Elimination, Arch. Int. Med. **32**:779 (Nov.) 1923.

by Bromer and Blumgart.[5] This view signifies, by way of illustration, that a patient who has received 300 minims (18.48 cc.) of tincture of digitalis in twenty-four hours will excrete more during the following day than one who has received only 50 minims (3.08 cc.). Although the statement may appear self-evident to some, it is at variance with the quite prevalent view that patients excrete about from 20 to 30 minims (1.2 to 1.8 cc.) of the tincture daily regardless of the quantity above these doses that is given.[6]

The practical importance of a clear differentiation of the two views lies in the fact that both are employed as a basis for statements regarding the dosage of digitalis which are mutually contrary. Those holding the latter view maintain that it is irrational to attempt to digitalize patients from the start with daily doses of the size of the so-called excretion doses, because such quantities are in themselves too small to produce the full effects, and because their continued use would fail to result in cumulation. With the premise being a fixed quantity of excretion daily, this conclusion seems reasonable. It is, however, contrary to the experience of many who have found that some patients can be satisfactorily digitalized by the continued use of daily doses as small as 30 minims of the tincture. The former view, which is supported by this study, is, on the other hand, in harmony with this experience, as well as with the results of the work of Gold and DeGraff [7] on the dosage of digitalis which show that the full therapeutic effects can be induced in the average ambulatory patient, although it takes longer, by the daily administration of quantities as small as from 3 to 4 grains (from 0.2 to 0.26 Gm.) of the drug, and that this dosage can then be continued for many months as the daily maintenance dosage without the occurrence of toxic symptoms. The explanation of this experience is that the patient who can eliminate 30 minims of the tincture daily after some of the drug has accumulated is unable to eliminate that dose daily at the start. In more general terms, this signifies that the cumulation of digitalis is a self-limiting process. As we have already shown, this fact can be demonstrated in only a restricted range of dosages. If the doses are too small, cumulation will cease at a level which fails to cause perceptible effects. If the doses are too large, toxic symptoms may be produced before a level is reached.

5. Bromer, A. W., and Blumgart, H. L.: The Maintenance Dose of Digitalis, J. A. M. A. **92**:204 (Jan. 19) 1929.

6. Pardee, H. E. B.: The Continued Use of Digitalis, New York State J. Med. **22**: 131 (March) 1922.

7. Gold, H., and DeGraff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients. IV. Newer Principles of Digitalis Dosage, J. A. M. A. **95**: 1237 (Oct. 25) 1930.

It should be emphasized that the observations made in this study are to serve to explain the successful use of small doses in digitalization and to point out the cause of some contradictions found in the literature. This is not intended as a plea for the use of small doses as a routine, particularly for patients with advanced congestive heart failure for whom there can be no question that more rapid digitalization by the use of larger doses at first and smaller doses subsequently for maintaining effects is the more desirable procedure.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

II. RELATIONSHIP OF LEFT VENTRICULAR HYPERTROPHY, THE WIDTH OF THE CARDIAC MUSCLE FIBER AND HYPERTENSION IN THE RAT

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It has long been recognized that hypertension is commonly accompanied by enlargement of the left ventricle. The cause for cardiac hypertrophy has been studied in recent years and the condition appears to be due solely to hypertrophy of the individual fibers rather than to hyperplasia. If this is correct, it would seem that some direct relationship between the height of the blood pressure, the degree of left ventricular enlargement and the width of the muscle fiber should exist. However, there has been surprisingly little study to establish such a relationship. To date the number of observations is insufficient to permit the application of statistical methods to this problem.

Pässler and Heinecke,[1] in their classic study of the relationship between cardiac hypertrophy and hypertension in partially nephrectomized dogs, employed the ratio of the weight of the left ventricle to the weight of the right ventricle as an index of hypertrophy of the left side. By this method they found that hypertrophy of the left ventricle accompanied hypertension, but their method of separation of the ventricles for weighing was obscure. They did not measure the individual cardiac muscle fibers.

The outstanding contribution to the subject of the rôle of the cardiac muscle fibers in cardiac hypertrophy and atrophy in man was made by Karsner, Saphir and Todd.[2] They selected one normal, one hypertrophied and one atrophic human heart for microscopic study and

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From the Laboratory of Physiological Chemistry of the University of Virginia.

1. Pässler and Heinecke: Versuche zur Pathologie des Morbus brightii, Verhandl. d. deutsch. path. Gesellsch. **9**:99, 1905.

2. Karsner, H. T.; Saphir, Otto, and Todd, T. W.: Cardiac Muscle in Hypertrophy and Atrophy, Am. J. Path. **1**:351 (July) 1925.

measurement. The hypertrophied heart was obtained from a patient who died of chronic nephritis. It was found that cardiac hypertrophy was due principally to enlargement of the fibers without hyperplasia, and that the fibers in the hypertrophied heart were appreciably wider, on the average, than those in the normal heart. A sufficient number of fibers was measured to permit statistical analysis. Atrophy was likewise shown to be due partially to a reduction in the size of the fibers. Since only one hypertrophied heart was studied, it was obviously impossible to show that the enlargement of the fibers was proportional to the hypertension or to the cardiac enlargement.

By assuming that an increase in the width of the fibers is an indication of cardiac hypertrophy, Mark and Geisendörfer [3] demonstrated cardiac hypertrophy in five partially nephrectomized dogs. The readings of the blood pressure in these animals were above normal. Since only a small number of observations was available, no conclusive relationship between the blood pressure and the width of the fibers could be deduced. These workers expressed the opinion that hypertrophy began in the left ventricle and eventually involved the right ventricle, but the evidence which they offered for this conception is not convincing.

A recent interesting observation on the width of fibers has been made by Harrison, Ashman and Larson.[4] They compared the pulse rate with the width of the fibers in several species of normal animals and found the slower heart rates associated with relatively thick fibers and, conversely, the faster rates with relatively thin fibers. The rat had the fastest rate and the thinnest fibers of all the species investigated.

During the last few years a series of experiments on partially nephrectomized rats has been conducted in this laboratory.[5] Hypertension, cardiac and renal hypertrophy, retention of nitrogen and polyuria were produced in these animals. In the experimental animals it was shown that there was a high statistical correlation between the height of the blood pressure and the $\frac{\text{heart weight}}{\text{surface area}}$ ratio. It should be pointed out that the hypertension was dependent on one factor, namely, an experimentally produced renal insufficiency. The possi-

3. Mark, R. E., and Geisendörfer, H.: Untersuchungen über die Nierenfunktion: Zur Frage des Zusammenhanges von Nierenmasse, Herzhypertrophie and Blutdrucksteigerung, Ztschr. f. d. ges. exper. Med. **74**:350, 1930.

4. Harrison, T. R.; Ashman, R., and Larson, R. M.: Congestive Heart Failure: XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, Arch. Int. Med. **49**:151 (Jan.) 1932.

5. Chanutin, Alfred, and Ferris, E. B., Jr.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diet, Arch. Int. Med. **49**:767 (May) 1932.

bility of an additional correlation between the blood pressure, the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers suggested itself. Accordingly, additional partially nephrectomized animals were studied in sufficient numbers to permit statistical analysis.

METHODS

The cardiac tissue was chosen at random from experimental animals. These animals were subjected to two-stage operations during which approximately 80 per cent of the total tissue of the kidney was removed. Animals which represented graded blood pressures were selected for study. Unilaterally nephrectomized and intact laparotomized animals were included in this series. All animals were mature and in good condition when they were killed. A variety of diets (table 1) was fed to the experimental rats.

TABLE 1.—*Diets Fed Experimental Animals*

Diet	Whole Liver, Gm.	Dried Extracted Liver, Gm.	Dried Extracted Beef, Gm.	Liver Extract, Cc.*	Lard, Gm.	Cod Liver Oil, Gm.	Starch, Gm.	Yeast, Gm.	Salt Mixture, Gm.	Cholesterol, Gm.	Uric Acid, Gm.	Sodium Bicarbonate, Gm.
1	20	..	..	..	14	5	52	5	4	..	..	..
2	40	..	..	..	16	5	30	5	4	..	..	..
3	60	..	..	..	14	5	12	5	4	..	..	..
4	80	..	..	..	6	5	..	5	4	..	..	..
5	..	80	..	..	6	5	..	5	4	..	..	..
6	..	..	80	..	10	4	..	6	4	..	..	..
7	..	..	20	30	..	5	37	4	4	..	..	..
8	10	..	..	..	14	5	62	5	4	..	..	..
9	15	..	..	..	18	5	53	5	4	..	..	..
10	..	..	20	..	16	5	50	5	4	..	..	..
11	..	..	20	..	14	5	47	5	4	..	5	..
12	..	..	20	..	10	5	44	5	4	..	..	10
13	..	..	20	..	13	5	50.5	5	4	2.5	..	..

* 30 cc. is equivalent to a concentrated extract of 225 Gm. of raw liver.

The method of obtaining the blood pressures has been described in a previous paper.[5] The carotid artery was cannulated in the rat anesthetized with ether, and the final reading was taken while there was a corneal reflex, but before there was any struggling.

For histologic study the hearts were fixed in Zenker's fluid to which solution of formaldehyde had been added, embedded in paraffin and sectioned at 6 microns. Some hearts were sectioned longitudinally so as to include only the left ventricle. In others, small portions were cut at different angles and levels so as to include both the right and the left ventricle. No effort was made to study any particular section of the right or the left ventricle, since the width of the fibers at different levels seemed uniform.

An attempt was made to measure the width of the longitudinally cut fibers at the nucleus with a filar micrometer, but this procedure was found extremely difficult. Accordingly, a more convenient method for measuring the width of the fibers was designed. The microscope was tilted to a horizontal position, and a powerful Leitz microscope lamp was used as a source of illumination. The section to be studied was held in a mechanical stage and the image thrown on a screen 18 inches (45.72 cm.) from the eyepiece of the microscope. A high, dry lens was used. The field was magnified 740 times by this arrangement. This was done in a dark room. Satisfactory fields for study were easily found. The widths

of the projected fibers were measured in centimeters with accurate calipers. Duplication was carefully avoided. These measurements were readily transposed into microns. Every fiber which had its nucleus well centered and its edges well outlined was measured.

In this series the weight of the heart represents the right and left ventricles after the atria were removed. It is realized that absolutely accurate weights of the remaining ventricles could not be obtained because of the difficulty in removing the atria.

In the statistical analysis of the measurements, standard formulas for standard deviation, correlation coefficient and probable error were used.

RESULTS

The pertinent data are presented in table 2. They are arranged in the order of increasing blood pressures (first column). The third, fourth and fifth columns show, respectively, the average widths of the fibers, representative standard deviations and the numbers of fibers counted in the left ventricles. Corresponding data for the right ventricles are given in the sixth, seventh and eighth columns. Because of the consistency of the figures obtained for the right ventricle, no effort was made to study all the hearts. The method of sectioning the right ventricle permitted a relatively small number of counts to be made, but the uniform average figures and their standard deviations seem to indicate a good index of reliability.

An analysis by standard deviations of the measurements of the fibers of the left ventricle of a control animal (rat 535) indicated that 68 per cent of all readings lay between 13.34 and 15.66 microns. On the other hand, fibers from a hypertrophied heart (rat 650) showed a variation between 19.20 and 25.42 microns. Comparison of the frequency distribution [6] for the control and the hypertrophic hearts showed significant differences, which are illustrated in table 3. The majority of the measurements of the widths of the individual fibers of the left ventricles of the control hearts fall within a very narrow range (from 0.85 to 1.30 cm.). This is in contrast to the wide range of frequency (from 1 to 2.30 cm.) seen in the hypertrophic hearts. An interesting observation which should be emphasized is that the fibers of the right ventricle are consistently smaller and fall within a narrower range of frequency than those of the left ventricle, regardless of the blood pressure; in other words, the fibers of the right ventricle in hypertension are narrower than the normal fibers of the left ventricle (tables 2 and 3). Karsner and his associates [2] also noted the greater frequency distribution in the hypertrophic heart. This may be due, in part, to the

6. Frequency distribution refers to the total frequency of the fibers included in each step-interval (0.05 cm.). For example, for the left ventricle of rat 535, twelve fibers are included in the step-interval from 0.95 to 1 cm., or from 12.84 to 13.51 microns.

Fig. 1 (rat 677).—Section of the left ventricle, showing the typically normal width of the fibers under an oil immersion lens; × 900.

Fig. 2 (rat 622).—Section of the left ventricle, showing the typically enlarged width of the fibers under an oil immersion lens; × 900.

TABLE 2.—*Results of Experimentation*

Systolic Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Left Ventricle: Width of Fiber, Microns	Left Ventricle: Standard Deviation	Left Ventricle: Fibers Counted	Right Ventricle: Width of Fiber, Microns	Right Ventricle: Standard Deviation	Right Ventricle: Fibers Counted	Rat	Weight, Gm.	Duration of Experiment, Days	Age at Death, Days	Diet (Table 1)	Procedure*
106	0.187	15.3	....	50	12.5	1.33	27	87	192	112	398	10	C (2)
110	0.176	16.4	....	54	11.8	....	24	335	259	4	335	10	C (2)
112	0.166	14.3	1.96	50	12.0	0.91	27	20	192	133	334	10	C (2)
116	0.202	16.2	....	70	12.5	1.92	25	75	255	140	256	10	C (2)
116	0.185	14.4	....	60	12.7	1.48	22	543	252	97	337	10	C (2)
118	0.205	14.2	....	60	12.9	....	39	135	302	207	246	10	C (2)
118	0.203	15.7	1.64	84	....	....	..	648	160	68	141	10	C (2)
120	0.192	14.6	....	44	....	....	..	311	212	12	241	10	C (2)
120	0.178	14.5	....	57	....	....	..	23	160	136	327	10	C (2)
122	0.190	15.2	....	76	....	....	..	615	306	104	176	2	C (2)
124	0.179	15.1	....	30	....	....	..	106	208	174	223	10	Op
124	0.161	14.9	1.62	74	....	....	..	650	144	95	156	5	Op
126	0.172	15.3	....	70	11.8	1.11	27	19	225	133	326	10	Op
126	0.222	18.2	....	46	....	....	..	601	223	42	207	10	Op
126	0.174	15.5	....	79	....	....	..	677	256	47	122	2	Op
130	0.199	15.3	....	89	....	....	..	653	217	68	137	1	C (2)
130	0.175	15.3	1.60	83	....	....	..	655	260	68	129	4	C (1)
132	0.180	14.9	1.62	87	....	....	..	577	197	107	182	4	C (2)
132	0.203	14.9	....	95	....	....	..	606	295	148	216	2	Op
134	0.208	19.7	....	63	14.0	....	32	587	329	37	274	10	Op
136	0.200	17.0	....	64	12.2	....	20	35	306	213	520	10	C (2)
136	0.163	14.5	1.16	70	....	....	..	535	177	133	190	6	C (2)
138	0.183	16.0	....	61	12.7	....	27	14	286	167	234	10	C (2)
138	0.192	17.5	1.89	101	....	....	..	533	303	113	182	4	C (2)
138	0.182	14.7	....	105	....	....	..	690	207	47	123	3	C (1)
140	0.187	20.3	....	69	12.7	....	31	175	301	99	153	10	C (2)
142	0.197	18.4	....	33	....	....	..	593	149	40	120	10	Op
142	0.165	15.0	1.62	90	....	....	..	522	208	140	196	12	Op
142	0.187	15.6	....	99	....	....	..	589	267	69	136	3	Op
144	0.196	17.3	2.02	72	....	....	..	521	273	140	196	12	Op
145	0.183	14.2	....	50	....	....	..	90	188	79	289	10	C (2)
146	0.197	17.8	1.55	87	....	....	..	656	274	68	129	4	Op
146	0.199	17.5	....	95	....	....	..	599	285	107	181	3	Op
147	0.202	18.3	....	39	....	....	..	432	98	10	154	10	Op
148	0.191	20.5	....	64	....	....	..	1231	180	98	174	11	Op
150	0.215	20.0	....	78	12.9	....	30	585	299	37	274	10	Op
150	0.165	17.7	1.62	49	....	....	..	594	162	139	303	3	Op
152	0.218	20.5	2.43	26	....	....	..	879	222	28	100	7	Op
153	0.204	17.4	1.62	84	....	....	..	524	344	140	196	12	C (2)
154	0.270	19.3	....	60	....	....	..	570	208	72	195	10	Op
156	0.287	20.7	....	58	12.5	1.42	25	478	228	91	246	10	Op
158	0.226	19.2	1.81	45	....	....	..	450	188	164	201	7	Op
160	0.201	20.0	2.50	107	....	....	..	691	248	47	117	4	C (1)
160	0.233	19.6	....	24	....	....	..	1326	122	160	229	9	Op
162	0.257	20.7	2.48	70	....	....	..	786	128	241	305	8	Op
164	0.217	21.2	2.68	33	....	....	..	536	265	176	220	7	Op
164	0.250	19.5	....	58	....	....	..	484	212	177	235	12	Op
164	0.184	19.6	....	97	....	....	..	676	215	47	122	2	Op
166	0.256	20.9	....	73	14.7	....	26	918	246	226	286	1	Op
166	0.219	21.2	2.39	36	14.6	....	25	928	248	210	289	13	Op
168	0.267	20.2	....	50	14.5	....	30	785	132	241	305	8	Op
170	0.264	20.4	....	86	....	....	..	534	200	133	190	6	Op
170	0.258	19.4	....	66	12.8	1.51	26	552	278	96	244	10	Op
172	0.247	19.3	....	75	12.5	....	24	425	292	43	267	10	Op
172	0.234	19.3	....	31	....	....	..	576	174	90	260	10	Op
174	0.238	19.3	2.57	55	12.5	1.18	23	59	144	121	201	10	Op
174	0.203	20.5	....	88	....	....	..	679	157	47	122	2	Op
176	0.221	20.2	1.38	31	....	....	..	633	214	196	281	1	Op.
178	0.261	21.6	....	60	12.7	1.42	15	479	262	109	269	10	Op
178	0.264	18.8	2.03	39	....	....	..	714	212	92	162	2	Op
180	0.258	21.4	....	60	11.8	....	17	465	328	113	320	10	Op
180	0.213	20.7	....	38	....	....	..	504	245	112	191	10	Op
184	0.296	22.6	....	73	11.3	1.47	24	439	338	133	272	10	Op
186	0.254	19.2	....	50	....	....	..	532	256	123	231	10	Op
187	0.205	20.8	....	54	12.4	....	26	455	362	105	333	10	Op
188	0.211	20.1	....	74	....	....	..	407	247	182	226	1	Op
190	0.308	19.8	....	59	....	....	..	97	158	200	415	10	Op
190	0.229	21.6	1.96	49	....	....	..	449	185	164	201	7	Op
192	0.244	22.4	....	50	12.4	0.95	22	433	303	122	257	10	Op
194	0.248	21.9	2.72	81	....	....	..	622	227	72	134	4	Op
194	0.208	22.0	2.25	35	15.0	....	..	700	...	...	...	10	Op
196	0.238	20.8	....	40	....	....	..	466	356	116	355	10	Op
198	0.212	18.9	....	43	....	....	..	500	...	...	...	10	Op
198	0.242	21.7	2.41	26	....	....	..	600	...	...	...	10	Op
200	0.265	22.2	....	47	12.7	1.51	30	505	188	115	192	10	Op
200	0.242	22.3	3.12	121	....	....	..	650	189	68	137	1	Op
212	0.281	21.9	2.24	45	....	....	..	529	293	87	150	2	Op
214	0.248	22.2	....	47	....	....	..	166	248	170	238	10	Op
230	0.310	23.6	4.45	64	....	....	..	163	207	225	293	10	Op

* C (1) indicates unilateral nephrectomy; C (2), both kidneys intact; Op, approximately 80 per cent of total kidney tissue removed.

difficulty of obtaining sections through or sufficiently close to the center of the nucleus of the large fibers, as well as to the unquestionable difference in the size of the individual fibers.

Early in this study it was suggested that there might be a quantitative relationship between the breadth of the fibers of the left ventricle and the blood pressure. In many cases a preliminary glance at several fields of a section allowed the observer to approximate the blood pressure

TABLE 3.—*Frequency Distribution of the Width of the Fibers*

Width of Fibers (Arbitrary Units)		Number of Fibers			
		Left Ventricle		Right Ventricle	
Centimeters (Magnification × 740)	Microns	Control	Hypertrophic Heart	Control	Hypertrophic Heart
0.65	8.78	0	0	1	0
0.70	9.47	0	0	1	0
0.75	10.15	0	0	5	3
0.80	10.80	0	0	5	0
0.85	11.49	1	0	3	9
0.90	12.19	1	0	7	8
0.95	12.84	12	0	5	3
1.00	13.51	13	1	3	4
1.05	14.18	15	0	2	1
1.10	14.87	12	0	2	0
1.15	15.56	9	2	1	1
1.20	16.23	5	1	1	0
1.25	16.90	2	3	1	0
1.30	17.56	0	7	0	1
1.35	18.24	0	5	0	0
1.40	18.92	0	6	0	0
1.45	19.60	0	8	0	0
1.50	20.23	0	9	0	0
1.55	20.95	0	10	0	0
1.60	21.60	0	11	0	0
1.65	22.33	0	8	0	0
1.70	22.92	0	9	0	0
1.75	23.60	0	7	0	0
1.80	24.30	0	9	0	0
1.85	24.98	0	7	0	0
1.90	25.68	0	4	0	0
1.95	26.35	0	5	0	0
2.00	27.02	0	3	0	0
2.05	27.70	0	2	0	0
2.10	28.40	0	1	0	0
2.15	29.10	0	1	0	0
2.20	29.70	0	0	0	0
2.25	30.40	0	1	0	0
2.30	31.09	0	0	0	0
		Rat 535	Rat 650	Rat 75	Rat 505

of the animal with surprising accuracy. An examination of figures 1 and 2 shows the typical differences seen in a control and in a hypertrophic heart. A statistical analysis of the data for the blood pressure and the width of the fibers of the left ventricle gave a correlation coefficient and probable error of 0.795 ± 0.027. These figures denote a "high relationship" between the two factors studied. The individual data are plotted in figure 3.

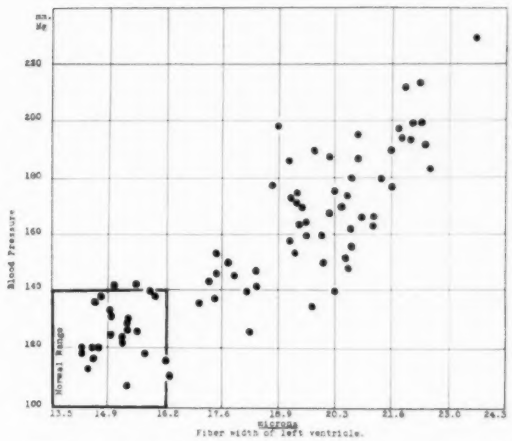

Fig. 3.—High relationship between the blood pressure and the width of the fibers of the left ventricle.

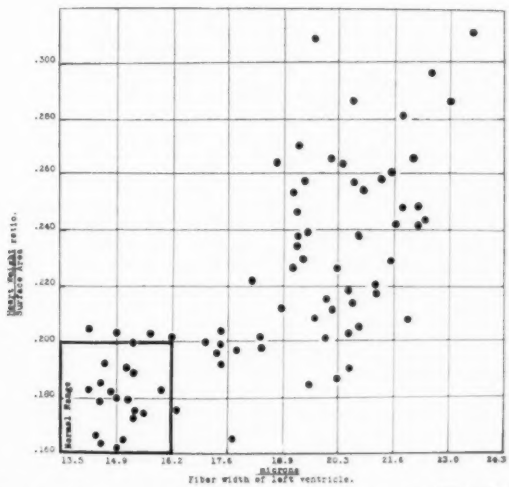

Fig 4.—Substantial or marked relationship between the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers of the left ventricle.

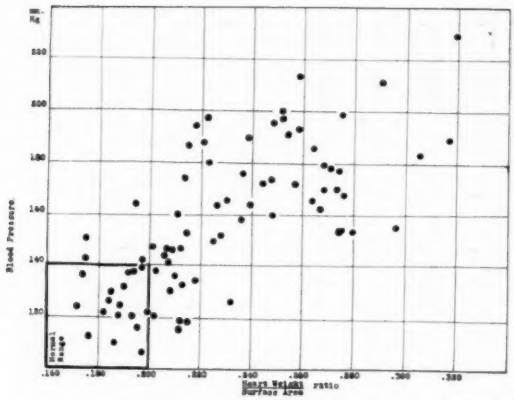

Fig. 5.—Relationship between the blood pressure and the $\frac{\text{heart weight}}{\text{surface area}}$ ratio.

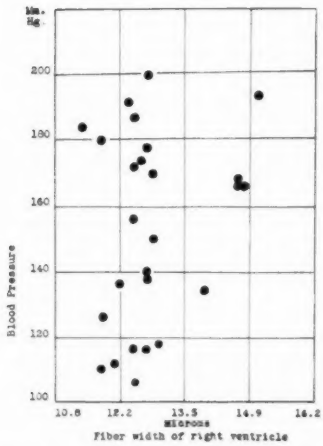

Fig. 6.—Lack of correlation between the blood pressure and the width of the fibers of the right ventricle.

Since it is common practice among pathologists to use the weight of the heart as an indication of hypertrophy, the correlation coefficient and its probable error for the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers of the left ventricle were calculated and found to be 0.690 ± 0.039. These figures represent the upper limits of a "substantial or marked relationship." The detailed data are presented in figure 4.

In a previous paper,[5] a high positive relationship (correlation coefficient and probable error $= 0.86 \pm 0.028$) was shown to exist between the blood pressure and the $\frac{\text{heart weight}}{\text{surface area}}$ ratio. By using additional measurements to study this relationship, the correlation coefficient of

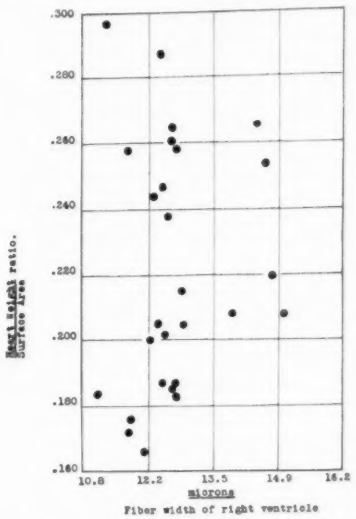

Fig. 7.—Lack of correlation between the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers of the right ventricle.

0.75 ± 0.027 was obtained. Although these figures have been lowered, they are still within the range of a very high relationship. A detailed presentation of these measurements is given in figure 5.

A study of the measurements shown in figure 6 demonstrates a total lack of correlation between the blood pressure and the width of the fibers of the right ventricle. The same fact holds true for the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers of the right ventricle (fig. 7).

COMMENTS

The objections that may be raised against the procedure used for obtaining the systolic blood pressures in our rats are: (1) the use of an

anesthetic, (2) the operation that is necessary for isolating the carotid and (3) the inability to obtain more than one reading of the blood pressure. It is believed that the statistical analyses given justify this method of obtaining the blood pressures. Furthermore, the assumption is reasonable that the blood pressure remains constant within a very narrow range of fluctuation during any given period. It is also apparent that the relationships pointed out between the blood pressure, the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers are independent of the time necessary for the development of the various stages of hypertension and cardiac hypertrophy.

There are several observations that may be of importance in determining cardiac hypertrophy in man and in the experimental animal at autopsy. The weight of the heart may or may not be an accurate index of hypertrophy, since the size of the organ is dependent to a great extent on the weight or the surface area of the animal. For example, two rats used as controls, weighing 170 and 340 Gm., had hearts weighing 0.495 and 0.760 Gm., respectively, but the $\frac{\text{heart weight}}{\text{surface area}}$ ratios were the same. With high blood pressure the smaller rat may have a heart the weight of which may approach that of the heart of a larger control animal. From these observations it seems logical to assume that the weight of the heart should be related to some unit such as the body weight or the surface area.

Since there is a marked degree of constancy in the width of the fibers of the left ventricle of the control rat, and since hypertension is accompanied by a positive deviation from the control values, it is suggested that similar studies be applied to other species. Karsner and his associates [2] emphasized the increased width of the cardiac fibers as a criterion for the demonstration of cardiac hypertrophy in human beings. An approach to the problem of recognizing cardiac hypertrophy should be feasible through a study of the width of the cardiac fibers.

SUMMARY

A series of seventy-nine experimental rats in which the blood pressures varied from 106 to 230 mm. of mercury was studied in an effort to correlate the blood pressure, the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fiber of the left and the right ventricles.

A statistical analysis of the results demonstrated the following facts:

1. A high relationship between the blood pressure and the width of the fibers of the left ventricle (correlation coefficient and probable error $= 0.795 \pm 0.027$).

2. A substantial relationship between the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and the width of the fibers of the left ventricle (correlation coefficient and probable error $= 0.690 \pm 0.039$).

3. A high relationship between the blood pressure and the $\frac{\text{heart weight}}{\text{surface area}}$ ratio (correlation coefficient and probable error $= 0.750 \pm 0.027$).

4. A total lack of correlation between the width of the fibers of the right ventricle and the blood pressure or the $\frac{\text{heart weight}}{\text{surface area}}$ ratio.

In the control animals, the average width of the fibers of the right ventricle was less than that of the fibers of the left ventricle. There was no increase in the width of the fibers of the right ventricle in the hypertrophied hearts.

ELECTROCARDIOGRAPHIC STUDY OF CORONARY OCCLUSION

FURTHER OBSERVATIONS ON THE USE OF CHEST LEADS

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When acute coronary occlusion is produced in the dog, the conventional limb leads often yield an inadequate record of the change which takes place in the action current of the heart. However, when electrodes are applied in certain positions on the wall of the chest, clearly significant electrical disturbances can be recorded which may be partly or completely missed in the tracings of the limb leads.[1] The electrocardiograms obtained from limb leads and chest leads supplement one another. If both are used together, a much more complete electrocardiographic picture of the effects of experimental coronary occlusion can be obtained.

These results in the dog suggested the use of chest leads in the study of acute coronary occlusion in man.[2] It was found that a similar situation presented itself: Chest leads yielded information that could not be obtained from limb leads. Moreover, it became evident that in certain cases this information was essential for correct electrocardiographic diagnosis. Since these observations were first made, thirty-six

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From the Robinette Foundation, Medical Division of the Hospital of the University of Pennsylvania, and from the Divisions of Cardiology and Pathology of the Philadelphia General Hospital.

1. Wood, F. C., and Wolferth, C. C.: An Electrocardiographic Study of Coronary Occlusion: The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Currents, J. Clin. Investigation **11**:815 (July) 1932; Experimental Coronary Occlusion: Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium; an Electrocardiographic Study, Arch Int. Med. **51**:771 (May) 1933.

2. (*a*) Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, Am. J. M. Sc. **183**:30 (Jan.) 1932; (*b*) Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, M. Clin. North America **16**:161 (July) 1932.

cases [3] of acute coronary occlusion have been studied with chest leads as well as with limb leads. Six have come to necropsy. The present paper consists of a discussion of the findings in these cases.

METHOD AND MATERIAL

Type of Electrodes.—Our early tracings [2a] were made by applying the ordinary large wrap electrodes of German silver to the chest, over pads moistened in warm salt solution. The use of copper disk electrodes 3.5 cm. in diameter and 1 cm. in thickness is less cumbersome, and is the method of choice at present. These electrodes are applied over small pads of absorbent cotton moistened in salt solution. They are held in position by adhesive tape, or by a light band of some resilient material encircling half the chest. It is essential that skin resistance be low enough to avoid distortion of the tracings. This can be effected by rubbing the skin with alcohol and by firm application of electrodes.

Leads Used.—The majority of the cases reported in this paper have been studied with three chest leads in addition to the conventional limb leads. The electrodes were applied as follows: The right arm electrode was placed on the anterior surface of the chest; the left arm electrode was placed on the posterior surface; the left leg electrode occupied its usual position on the left lower extremity. The exact positions are described in the next paragraph. For convenience, the anteroposterior lead is referred to as lead IV, as was done in a previous publication; [2a] the anterior-left leg lead is termed lead V, and the posterior-left leg lead is called lead VI. Further discussion of the relative usefulness of these three chest leads will be undertaken elsewhere in the paper.

Variations in the Tracing Obtained by Varying the Locations of the Electrodes.—Chart 1 *A* illustrates the electrocardiograms which were obtained for a normal person from electrodes situated at various designated points. When small electrodes are used, a relatively small change in the position of the anterior electrode may cause considerable alteration in the tracing. On the other hand, the posterior electrode can be moved in a comparable way without causing any definite change in the electrocardiogram.[4] In our studies, the posterior electrode has been placed at a point just below and mesial to the left scapular angle, with the arm at the side. The anterior electrode has been placed in two different positions: (1) at the apex of the heart and (2) at a point

3. These cases were obtained from the wards of the University of Pennsylvania Hospital, the Philadelphia General Hospital, the Mount Sinai Hospital and the Pennsylvania Hospital and from private practice.

4. This point has not been tested in a series of pathologic cases. It is possible that a large heart or a posterior infarct might give different results. However, in one case of probable posterior infarct, moving the posterior electrode produced no definite effect except to cause minor variations in lead VI.

4 cm. to the left of the sternum, in the fifth interspace. The latter point has been the one most frequently used in the past, but the apical position is probably the better of the two for studying most cases of coronary occlusion. The only difference in the tracings for the normal person is that when the electrode is placed at the apex the initial downward deflection of Q R S in leads IV and V is deeper and the upward deflection which follows may be smaller. In pathologic cases, however, especially in cases of presumable posterior infarction, the deviations of the RS-T interval which appear in leads IV and V may be slightly larger when the anterior electrode is over the apex. Care must be taken not to allow the anterior electrode to be displaced upward, to the right or too far beyond the apex to the left. Marked variations in the character of the tracing can occur if this source of error is not foreseen and prevented. In this connection it might be mentioned that the large electrodes used in the early stages of this study [2a] seem to be less subject to error. Small changes in position do not seem to cause marked alterations in the electrocardiogram. Moreover, the tracings are comparable to those obtained with small electrodes at or near the apex, although the Q R S complexes and T waves may be slightly smaller.

Normal Controls.— Chart 1 *B* illustrates the appearance of six leads for a normal person. A series of thirty normal persons has been studied. In leads IV and V, the P wave is often small, diphasic or inverted. The Q R S complex consists of a large initial downward deflection, usually followed by an upward deflection. The RS-T interval is often quite short, giving way rapidly to the deeply inverted T wave. In the tracings of all normal persons in which there has been no deviation of the RS-T interval in the limb leads, this interval has begun on the iso-electric line or within 1 mm. below it. Slight depressions of RS-T must be interpreted with caution; slight elevations of this interval are probably more significant. The T wave is definitely inverted for all our normal persons and is usually of considerable magnitude. The characteristics of lead VI and its normal variations seem to be similar to those of lead III.

Abnormal Variations in the Absence of Definite Cardiac Infarction. —Thus far, leads IV and V have shown the following variations: The initial downward deflection of Q R S may be absent in the tracings of certain patients with marked right axis deviation, of some persons with left bundle branch block (new nomenclature) and of some with evidence of myocardial disease without a definite history of coronary occlusion. This deflection may be small for some persons with left bundle branch block or for patients with lesser degrees of right axis deviation. The T wave has been upright for certain patients with myocardial disease. The RS-T interval is readily depressed below the iso-electric line as an artefact due to "overshooting." True deviations

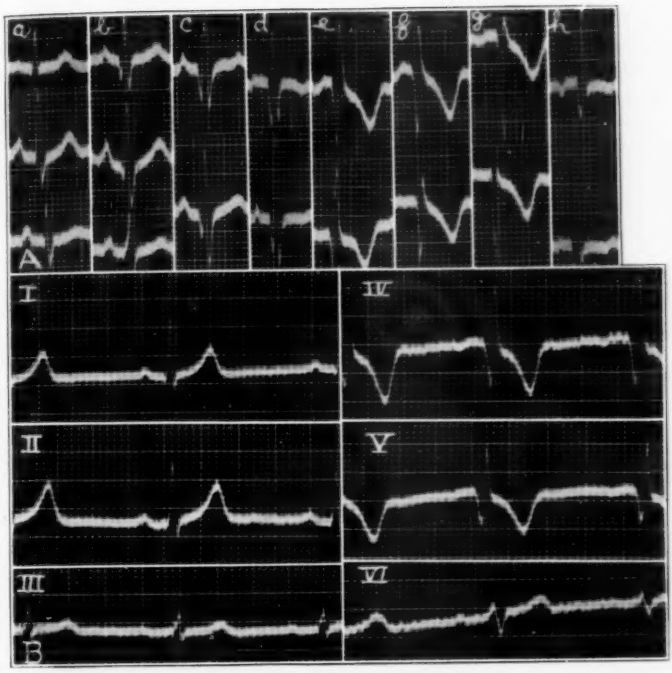

Chart 1.—*A*, electrocardiograms of a normal youth, aged 21, obtained by varying the position of the anterior electrode on the chest. For the sake of brevity, any anteroposterior lead is called lead IV. Lead V is any lead from the anterior surface of the chest to the left leg. Lead VI is the lead from the posterior surface of the chest to the left leg. *a*, indicates three limb leads; *b*, leads IV, V and VI—anterior electrode at the aortic area; *c*, leads IV and V—anterior electrode at the pulmonic area; *d*, leads IV and V—anterior electrode in the third left interspace, 4 cm. from the sternum; *e*, leads IV and V—anterior electrode in the fourth left interspace, 4 cm. from the sternum; *f*, leads IV and V—anterior electrode in the fifth left interspace, 4 cm. from the sternum; *g*, leads IV and V—anterior electrode just to the left of the apex pulse; *h*, leads IV and V—anterior electrotrode in the fourth right interspace, 2 cm. from the sternum.

At about the level of the fourth rib the tracing in this patient changes abruptly. The initial downward deflection of Q R S becomes more prominent; the terminal downward deflection disappears, and the T wave becomes deeply inverted.

B, six leads in a normal youth, aged 20. The anterior chest electrode was 2 cm. inside the apex impulse. The posterior chest electrode was just inside the angle of the left scapula. The initial downward deflection of Q R S in leads IV and V is prominent. It is followed by an upward deflection. The RS-T interval is short and begins at least 1 mm. below the iso-electric line. Therefore, small depressions of RS-T in leads IV and V when unassociated with other findings must not be stressed as diagnostically significant. Small elevations in RS-T may be more important. The T waves in leads IV and V are deeply inverted. Lead VI is somewhat like lead III with a deeper S wave.

of the RS-T interval are to be expected in all those conditions which produce them in the limb leads,[5] but are not always present in these conditions. They are therefore probably no more nor less pathognomonic of recent cardiac infarction than are similar deviations in the three conventional leads. In the absence of acute infarction, we have seen such deviations in leads IV and V of persons with acute rheumatic myocarditis, of persons with left bundle branch block and of certain patients with presumably damaged hearts who were given digitalis.[6] The dose of digitalis required to produce them seems to be smaller in old than in young persons. One patient, aged 78, showed a depression of the RS-T interval in lead IV after taking 32 cc. of the tincture in eight days. In this case, however, the persistence of the initial downward deflection helped to differentiate the condition from the cases of cardiac infarction to be described later.

The abnormal variations in lead VI are similar to those seen in lead III.

CASES OF CARDIAC INFARCTION WITH ELECTROCARDIOGRAPHIC STUDY AND NECROPSY

Case 3.—M. C., a white woman, aged 52, had been known to have a systolic blood pressure of about 200 mm. of mercury for at least four years. One year before admission she suffered an attack suggestive of coronary occlusion, and made a fairly satisfactory recovery. On March 16, 1932, she was again seized with a severe pain over the heart, associated with a reduction of blood pressure to 150 systolic and 100 diastolic. On March 17 she was admitted to the medical wards of the Philadelphia General Hospital, where a clinical diagnosis of acute coronary occlusion was made. She became progressively worse and died on March 26.

The electrocardiograms of this patient are shown in chart 2. There was nothing strikingly significant of recent cardiac infarction in the three limb leads in any one tracing, although on March 22 lead I showed a suggestion of elevation of the RS-T interval. Leads IV and V showed a marked depression of the RS-T interval throughout and an absence of the initial downward deflection of Q R S. The Q waves and inverted T waves in leads II, III and VI suggested the presence of an old posterior infarct.

Necropsy was performed by Dr. B. A. Gouley. The heart showed hypertrophy and considerable generalized coronary sclerosis. There was an old occlusion of the posterior descending branch of the right coronary artery, with an organized infarct and beginning cardiac aneurysm. This lesion involved the lower part of the posterior surface of the left ventricle, the posterior portion of the apex of the heart and the adjacent posterior section of the interventricular septum. A recent occlusion of the left anterior descending coronary artery was found, 1 cm. beyond its origin. An acute infarct was located in the distribution of this artery. It involved the anterior surface of the left ventricle, including the apex and the anterior part of the interventricular septum. It extended around the lateral surface

5. Wolferth, C. C.: Diseases of the Heart and Blood Vessels, in Progressive Medicine, Philadelphia, Lea & Febiger, 1931, vol. 3, p. 169.

6. Bellet and McMillan: Unpublished observations.

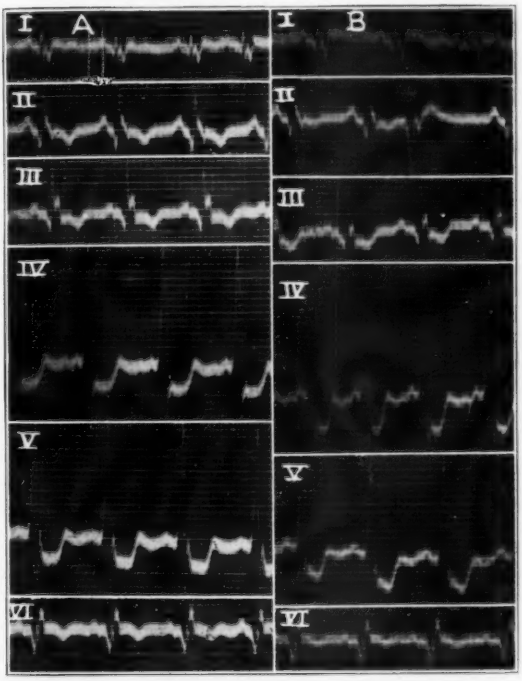

Chart 2.—Electrocardiograms of case 3, an example of group A. The anterior electrode was placed at the apex beat. Acute coronary occlusion occurred on March 16, 1932. *A*, six leads taken March 21, five days later. No definite changes of the RS-T interval are present in the limb leads. Depressions of the RS-T interval of 3 mm. are seen in leads IV and V. The initial downward deflection of Q R S in leads IV and V is absent. The occurrence of a Q wave and an inverted T wave in leads II, III and VI suggests the presence of a previous posterior infarct. At necropsy, an old posterior and a recent anterior infarction were found in the left ventricle.

B, six leads, taken March 23, seven days after the attack. A small elevation of the RS-T interval has appeared in lead I. The RS-T interval in lead III shows a suggestion of depression. In other respects, the tracing is much the same as the previous one. Leads IV and V show an absence of the initial downward deflection of Q R S and a 4 mm. depression of the RS-T interval.

of the heart, owing to obstruction of all the lateral branches of the anterior descending artery. A mural thrombus was adherent to the inner surface of the recent infarct. A rupture 2 cm. in length was found at about the middle of the lesion.

Summary.—A patient with an old posterior and recent anterior infarction presented an electrocardiogram with suggestive elevation of the RS-T interval in lead I, a definite depression of the RS-T interval in leads IV and V and an absent initial downward deflection in leads IV and V.

Case 4.—D. G., a white man, aged 42, was admitted to the Mount Sinai Hospital on Oct. 23, 1932, in a state of collapse. The day before admission while he was apparently well, he was seized with a severe pain over the heart. The pain continued. He became weak and vomited several times. On admission he was described as obese, pallid, dyspneic and cyanotic. The skin was moist. The cardiac rate was 140 per minute; the rhythm was regular. The blood pressure was 80 systolic and 70 diastolic. There were râles at each base. A diagnosis of acute coronary occlusion was made. The patient died on October 26.

An electrocardiogram was taken on October 25 (chart 3*A*). The RS-T interval was elevated in lead I and markedly depressed in leads IV and V. A Q wave was present in lead I. The initial downward deflection in leads IV and V was considerably diminished in size but was present.

Necropsy was performed by Dr. D. Meranze on October 26. The heart was moderately enlarged, weighing 500 Gm. There was an acute occlusion of the left anterior descending coronary artery, beginning just below the point of origin of the circumflex branch. An acute infarct involved the entire anterior surface of the left ventricle, the apex, the lateral wall, the anterior part of the interventricular septum and the lower fourth of the posterior wall. The pericardium over this lesion showed inflammatory changes. Mural thrombi were present in the left ventricle. The other coronary arteries were atheromatous but patent. An interesting anomaly in this patient was that the posterior wall of the left ventricle was supplied by the circumflex branch of the left coronary artery, not by the right coronary artery.

Summary.—The patient had acute occlusion of the left anterior descending coronary artery. An electrocardiogram taken on the third day showed an elevation of the RS-T interval in lead I and a marked depression of this interval in leads IV and V.

Case 5.—A. L., a white man, aged 55, was known to have had hypertension for five years. On May 28, 1932, he suffered a severe attack of pain over the heart. The pain subsided the next day, but his condition became progressively worse. He was admitted to the Philadelphia General Hospital seven days later (June 4) moribund. Dyspnea, cyanosis, low blood pressure (90 mm. of mercury systolic), cold moist skin, pulmonary congestion and tachycardia (130 per minute) were the striking features. He died on June 5.

An electrocardiogram was taken on June 4, seven days after the onset (chart 3*B*). Lead I showed the suggestion of an elevation of the RS-T interval. Leads IV and V showed slight depressions of this interval, but these depressions were much smaller than those usually seen in anterior infarction. There was no Q wave in leads II and III to suggest the presence of a previous posterior infarction.

Necropsy was performed by Dr. R. P. Custer. There was an old infarct in the lower half of the posterior wall of the left ventricle. A recent occlusion of the left anterior descending coronary artery was found 1.5 cm. from its origin. The

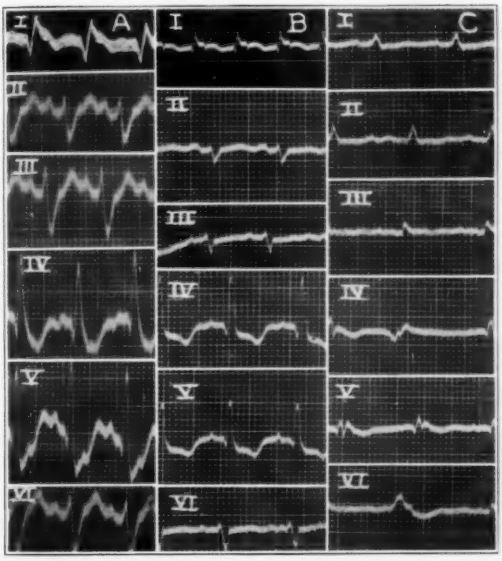

Chart 3.—*A*, electrocardiograms of case 4 taken Oct. 25, 1932, with the anterior electrode over the apex impulse. Acute coronary occlusion occurred October 22. The Q R S complexes are all widened and slurred. Lead I shows a Q wave and an elevation of the RS-T interval. Leads II and III show no changes in the RS-T interval. Leads IV and V show small initial downward deflections of Q R S and depressions of the RS-T interval. Lead VI resembles lead III. At necropsy, a recent infarction of the anterior surface of the left ventricle was found. This is an example of a case in group A.

B, electrocardiograms of case 5 taken on June 4, 1932, with the anterior electrode over the apex impulse. Acute coronary occlusion had taken place on May 28, one week previously. Lead I shows an RS-T interval elevation. Leads II and III show nonspecific findings. The Q R S complexes are small. In leads IV and V the initial downward deflection of Q R S is small. There is only a slight depression of the RS-T interval. Lead VI resembles lead III. At necropsy, an acute infarction of the anterior surface of the left ventricle was found.

C, electrocardiograms of case 34 taken on June 12. Acute coronary occlusion probably occurred on June 7, five days previously. All the Q R S complexes and T waves are small. No findings suggestive of acute coronary occlusion were noted. At necropsy, extensive old infarction was present in both the anterior and the posterior walls of the left ventricle. A small recent infarct, 2 cm. in diameter was found at the extreme apex of the heart.

acute infarction involved the lower two thirds of the anterior surface of the left ventricle, the apex and the anterior half of the interventricular septum. The recent thrombosis had not involved the main left lateral branches of the anterior descending coronary artery; consequently the infarct did not extend around the left lateral border of the heart.

Summary.—A patient with acute coronary occlusion showed only slight deviations of the RS-T interval in any of the six leads seven days after the onset. At necropsy, an old posterior and a recent anterior infarct were found.

Case 34.—J. S., a white man, aged 67, had suffered with dyspnea on exertion for more than a year. On June 7, 1932, he was suddenly seized with a severe pain in the epigastrium and the left hypochondrium, and became markedly short of breath. He was admitted to the Philadelphia General Hospital on June 12, acutely ill with urgent dyspnea, feeble heart sounds, a cardiac rate of 109 per minute and a blood pressure of 90 systolic and 70 diastolic. Congestion was present in the liver and the bases of the lungs. The patient became progressively worse and died on June 16.

Electrocardiograms were taken six, seven and eight days after the onset (chart 3 *C*). The complexes were all of extremely low amplitude. No characteristic deviation of RS-T were seen in any of the tracings.

Necropsy was performed by Dr. R. P. Custer. The heart showed extensive coronary sclerosis. An old occlusion of the right coronary artery was found 3 cm. from its origin. The entire posterior wall of the left ventricle was the seat of an old infarction. There was also an old occlusion of the left anterior descending artery with infarction of the anterior wall of the left ventricle and the formation of an aneurysm in its lower half. A small recent infarction, 2 cm. in diameter, was found at the extreme apex. Its surface presented downward toward the diaphragm. A mural thrombus was attached to its inner surface. The ventricular wall at this point was only 2 mm. thick. A large clot was found in the lower end of the aorta at its bifurcation. (The pain in the upper part of the abdomen was attributed to coronary occlusion rather than to the aortic thrombus.)

Summary.—A patient with extensive coronary sclerosis and with old infarcts in both the anterior and the posterior surfaces of the left ventricle suffered a small infarction at the extreme apex. Six days' later there was no deviation of the RS-T interval in any lead. The electrocardiographic complexes were small and bizarre, and yielded no diagnostic information concerning the recent infarct.

Case 19.—W. M. B., a white man, aged 54, was well until Oct. 16, 1932. On that day he experienced an attack of substernal pain radiating to both arms, lasting four hours. This was diagnosed coronary occlusion by his physician; the patient was kept in bed continuously from that time on. He had a brief attack of substernal discomfort on October 17. Then he remained free from pain until December 22 That evening about midnight he had another severe seizure lasting about four hours. He was admitted to the medical wards of the Hospital of the University of Pennsylvania on December 24, in the service of Dr. Alfred Stengel. He was apparently comfortable. The blood pressure was 160 systolic and 100 diastolic. The aortic second sound was accentuated. The heart was moderately enlarged. There were no evidences of congestive heart failure. The tentative diagnosis was: occlusion of several relatively small coronary arteries, coincident with the previous attacks of pain. At 4 a. m. on December 28, another attack began. This was more severe than any previous one, and lasted fourteen hours despite the repeated administration of morphine. There was a rise of temperature the next day. The leukocyte count was 14,000. The blood pressure dropped to

140 systolic and 110 diastolic. The pulse rate, which had been about 80 per minute, rose gradually to 110 per minute. A diagnosis of another coronary occlusion was made. Death occurred on December 30, at 5 a. m., during an attack of cardiac pain.

The electrocardiograms of this patient are shown in chart 4. The first tracing (December 24) showed no deviation of the RS-T interval. The findings were those of an old anterior infarct. The large T waves in leads IV and V suggested a possible small recent occlusion superimposed on the old one. The second electrocardiogram (December 27) showed no deviation of the RS-T interval, but the change which had taken place in the contour of the tracing in three days made us feel more certain that a recent small infarction had occurred. The third (December 28) and fourth (December 29) electrocardiograms showed unmistakable evidence that the attack on December 28 had been due to a large infarction in the anterior surface of the left ventricle.

Necropsy was performed by Dr. Parsons on December 30. The heart showed moderate enlargement. The posterior surface of the left ventricle was normal, and the arteries in that region were relatively free from sclerosis. There was marked sclerosis of the arteries on the anterior surface of the left ventricle. There was a recent red thrombus obstructing the left anterior descending coronary artery, 1.5 cm. from its origin. There was acute infarction of the lower two thirds of the anterior surface of the left ventricle. The left ventricular wall just above and mesial to the apex was thinned out and showed a slight bulge. This point was the seat of old infarction. In addition, one of the small lateral branches of the left anterior descending artery was obstructed by an organizing thrombus. The exact order of events could not be determined at necropsy. Nevertheless it was evident that a recent acute occlusion of the main left anterior descending coronary artery had taken place (probably on December 28), and that at least two smaller occlusions had previously occurred in the distribution of this artery.

Summary.—This patient probably suffered several attacks of coronary occlusion before coming to the hospital. An electrocardiogram on admission showed the findings of an old anterior infarction and certain indications that a small recent occlusion had taken place. On December 28, while the patient was in the hospital, another attack occurred. An electrocardiogram on that day showed an elevation of the RS-T interval in lead I and a depression in leads II and III. Leads IV and V showed an absence of the initial downward deflection of Q R S and a deep depression of the RS-T interval. Necropsy showed a recent occlusion of the main left anterior descending coronary artery and at least two small infarcts of less recent origin in the distribution of this artery.

Case 33.—H. R., a white man, aged 61, gave a history of an attack suggesting coronary occlusion in 1927. He then remained well until 11 a. m. on Jan. 4, 1933, when he was seized with intense pain in both arms extending from the shoulders to the finger-tips. He also had slight pain across the chest at the level of the clavicles. He was admitted to the medical wards of the Pennsylvania Hospital in the service of Dr. Arthur Newlin on January 4. On admission he was prostrated, sweating and weak. The pulse rate was 90 per minute. The blood pressure was 180 systolic and 130 diastolic. The liver was enlarged and tender. There were râles at the bases of both lungs. The next day, fever and leukocytosis were present, and the blood pressure dropped to 100 systolic and 75 diastolic.

The electrocardiographic studies are shown in chart 5. Leads II and III showed deep Q waves and elevations of the RS-T interval. Lead IV showed an absence of the initial downward deflection of Q R S and a slight elevation of the

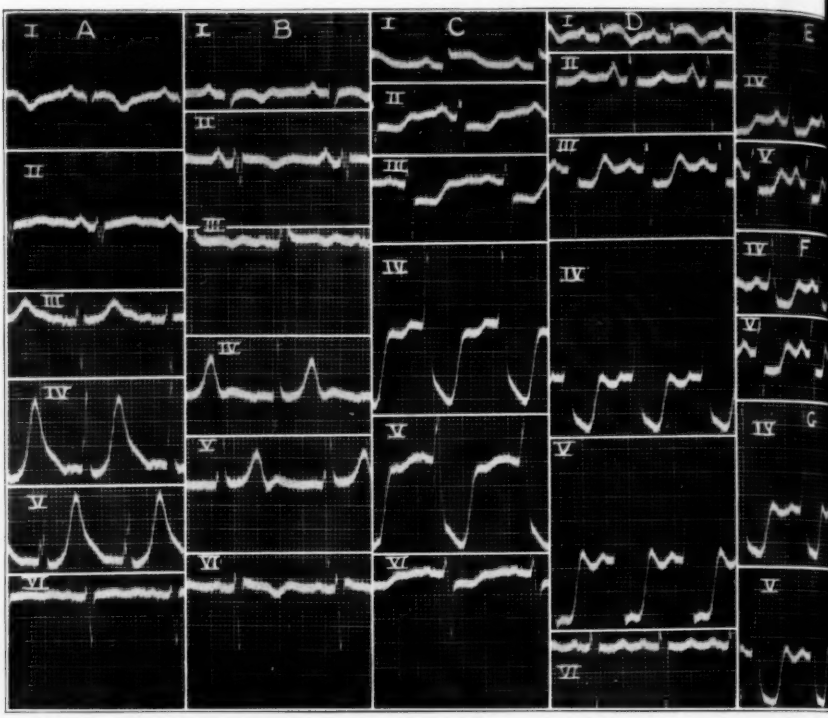

Chart 4.—Electrocardiograms of case 19; an example of group A. The anterior electrode was placed over the apex impulse. Attacks of cardiac pain occurred on Oct. 16, 1932, December 22 and December 28. Necropsy on December 30 showed recent occlusion of the main left anterior descending coronary artery, 1.5 cm. from its origin. In addition, several smaller, less recent infarctions were found in the distribution of this artery.

A, tracing taken on December 24. The inversion of T 1, the absence of the initial downward deflection of Q R S in leads IV and V, and the upright T waves in leads IV and V suggest the presence of an old infarction in the anterior surface of the left ventricle. The unusual height of the T waves in leads IV and V suggest the possibility that a recent small coronary occlusion (on December 22) has been superimposed on the old one (October 16).

B, tracing taken on December 27. The changes which have occurred since the previous tracing was taken strengthen the possibility that a recent small coronary occlusion has occurred. On December 28, at 4 a. m. another much more severe attack of cardiac pain began.

C, tracing taken December 28, six hours after the onset of pain. Definite elevation of the RS-T interval is seen in lead I. Depression of this interval appears in all the other leads. The initial downward deflection of Q R S in leads IV and V is absent.

D, tracing taken December 29. Some changes have taken place since the preceding day. The general features of the tracing are typical of group A.

E, leads IV and V taken December 29, with the anterior electrode at the aortic area.

F, leads IV and V (December 29) with the anterior electrode at the pulmonic area.

G, leads IV and V (December 29) with the anterior electrode in the third interspace, 4 cm. to the left of the sternum.

Deviations of the RS-T interval are recorded from all these positions, but become more marked as the anterior electrode approaches the point on the wall of the chest lying directly over the infarct. It may be possible in some cases to arrive at a rough estimation of the size of an anterior infarction by determining the size of the area in the precordium from which deviations of the RS-T interval are recordable.

RS-T interval. On the basis of these findings, combined with the history, a tentative diagnosis was made of old anterior and recent posterior infarction.

The patient died suddenly on January 8. Necropsy was performed by Dr. John Bauer on January 8. The heart was moderately dilated. There was an old infarct in the lower third of the anterior surface of the left ventricle. A recent occlusion of the right coronary artery was found, with acute infarction of the entire posterior surface of the left ventricle, not including the apex. There was a mural thrombus on the inner surface of the old infarct.

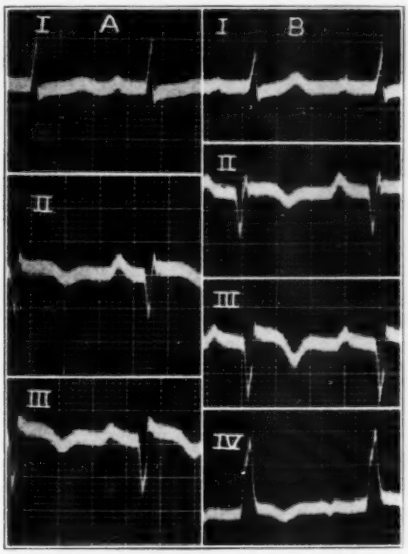

Chart 5.—Electrocardiograms of case 33, an example of group B. The anterior electrode was placed in the fifth interspace, 4 cm. to the left of the sternum. The patient had an attack suggesting coronary occlusion in 1927. Another attack of severe prolonged cardiac pain began on Jan. 4, 1933.

A, electrocardiogram taken January 5. Lead I shows little. Lead II shows a deep Q wave and a slight elevation of the RS-T interval. Lead III shows a deep Q wave, a more marked elevation of the RS-T interval and a more definitely inverted T wave. Leads IV, V and VI were not taken. The P R interval is 0.20 second.

B, electrocardiogram taken January 7. Leads I, II and III are much the same. The T waves in leads II and III are more definitely inverted. The P R interval is slightly longer (0.22 second). Lead IV shows an absence of the initial downward deflection of Q R S, a slurring of the R wave and a very slight elevation of the RS-T interval. Leads V and VI were not taken.

On the basis of these tracings and the clinical history, a diagnosis of old anterior and recent posterior infarction was made ante mortem. Necropsy confirmed the diagnosis.

Summary.—The electrocardiogram of a patient with an old anterior and recent posterior cardiac infarction presented a deep Q wave and an elevation of the RS-T interval in leads II and III. Lead IV showed an absence of the initial downward deflection of Q R S and a slight elevation of the RS-T interval.

ELECTROCARDIOGRAPHIC CLASSIFICATION OF CASES

The great majority of our thirty-six cases of acute coronary occlusion fit into one or the other of the following two electrocardiographic groups:

Group A (Nineteen Cases).—Examples of this type are shown in charts *2*, *3 A*, 4, *6*, *7* and 8 and in the two cases reported previously.[2a] The characteristics of the group may be defined under the heads of the various leads.

Lead I: In the first days the RS-T interval may be elevated. (However, in nine of the nineteen cases, this elevation was absent in at least one tracing during the first week, when chest leads showed definite deviations of the RS-T interval [charts *2*, *7* and 8].) The elevation of the RS-T interval soon subsides as a rule, and in most cases inversion of the T wave appears. This change from a deviation of the RS-T interval of one direction to a T wave of the opposite direction usually takes place more rapidly in lead I than in leads IV and V. A Q wave was present in lead I in six of the nineteen cases.

Lead II: Usually no deviation of the RS-T interval is seen in this lead. If one appears it is likely to be an elevation (exception case 19, chart 4). The shape and appearance of the T wave is not constant. No findings that can be recognized as diagnostically helpful appear in the later stages; but if the RS-T interval has been elevated in the acute stage, an inversion of the T wave may appear later.

Lead III: This lead likewise seldom shows a deviation of the RS-T interval. In occasional cases there is a depression of this interval. The subsequent changes seem nonspecific for diagnostic purposes, in the light of present knowledge.

Lead IV: In this lead the findings are more striking[7] than in any other. There is a deep depression of the RS-T interval which usually persists for from five to nine days (i. e., much longer than the elevation in lead I). In the course of time it disappears. A high-peaked, upright T wave develops and tends to remain. The large initial downward deflection of the Q R S complex either disappears completely or is markedly diminished in size. In fourteen of nineteen cases it disappeared completely and did not return in the period during which we

7. The deviations of the RS-T interval and other deflections are probably magnified by the proximity of the anterior electrode to the heart.

were able to follow the patient. In one case it disappeared and returned slightly three months later (case 11). In four cases a small deflection persisted throughout, never more than 2 mm. in depth.

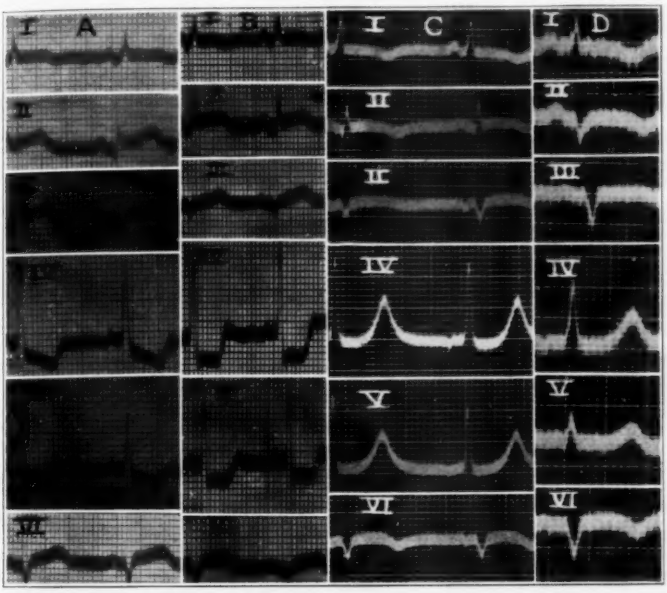

Chart 6.—Electrocardiogram of case 18, an example of group A. The anterior electrode was placed in the fifth interspace 4 cm. to the left of the sternum. Acute coronary occlusion occurred on March 15, 1932. *A*, tracing taken seven days later (March 22). Lead I shows little. Lead II shows an elevation of the RS-T interval. Lead III shows little. Leads IV and V show an absence of the initial downward deflection of Q R S and slight depressions of the RS-T interval—(more marked in lead IV). Lead VI is similar to lead III.

B, tracing taken on March 24. The limb leads have not changed a great deal. A much more definite depression of the RS-T interval is seen in leads IV and V, again more marked in lead IV.

C, tracing taken on March 30. The deviations of the RS-T interval have disappeared and T waves have appeared which are opposite in direction to the original deviations of the RS-T interval.

D, tracing taken April 29. The initial downward deflection of Q R S in leads IV and V has not returned. These last two tracings (*C* and *D*) show the characteristic findings of the later stages of this type of infarction.

Lead V: The findings in this lead are similar to those in lead IV, but the depression of the RS-T interval is usually less deep. All the complexes may be somewhat smaller.

Chart 7.—Electrocardiograms of case 12, an example of group A. The anterior electrode was situated at the apex. Acute coronary occlusion occurred Nov. 10, 1932.

A, tracing taken November 10, three hours after the attack. Lead I shows an elevation of the RS-T interval. Lead II shows little. Lead III shows a suggestive depression of the RS-T interval. Leads IV and V show an absence of the initial downward deflection of Q R S and marked depression of the RS-T interval. Lead VI is a rather unsatisfactory replica of lead III.

B, tracing taken November 11. There are no deviations of the RS-T interval in the limb leads. The Q R S complex and T wave in lead I have changed since the previous day. Leads IV and V still show marked depressions of the RS-T interval. The T wave is beginning to become upright.

C, tracing taken December 5. The deviations of the RS-T interval have practically disappeared. The initial downward deflection of Q R S in leads IV and V has not returned. The inverted T 1 and T 2 and large upright T 4 and T 5 are characteristic of the later stages of this type of infarction.

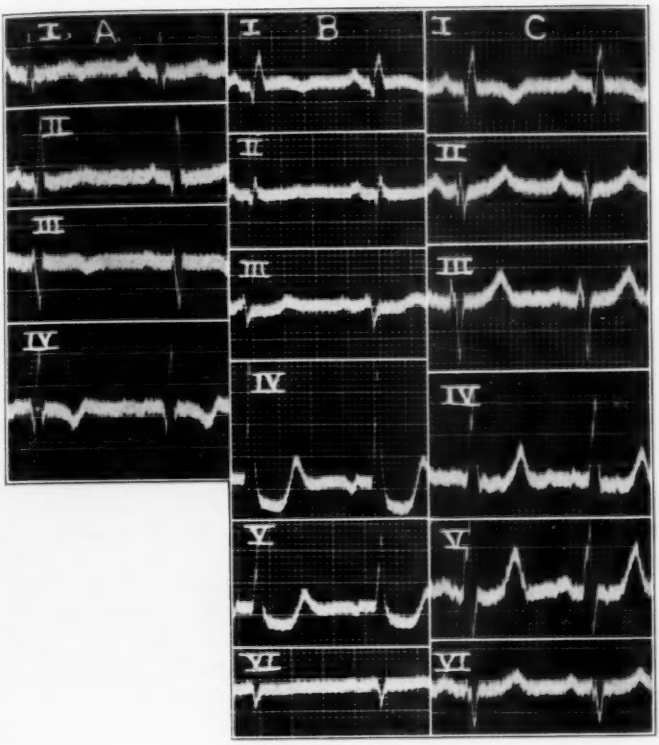

Chart 8.—Electrocardiograms of case 6, an example of group A. The anterior electrode was placed in the fifth left interspace, 4 cm. from the sternum. Acute coronary occlusion occurred on July 21, 1932.

A, tracing taken in February, 1932, five months before the attack.

B, tracing taken on July 25, four days after the attack. Lead I shows a Q wave and a cove-shaped RS-T interval, but there is no deviation of this interval from the iso-electric line. Leads II and III show little. Leads IV and V show a disappearance of the initial downward deflection of Q R S. Lead IV shows a definite depression of the RS-T interval. Lead V shows much less change in the RS-T interval. T 4 and T 5 are beginning to turn upward. Lead VI shows little.

C, tracing taken November 26, four months after the attack, showing the characteristic late findings of this type of infarct. The initial downward deflection of Q R S in leads IV and V has not returned. T 4 and T 5 are upright and large. There are a Q wave and an inverted T wave in lead I.

Lead VI: As a rule, this lead gives no additional information. It often, but not always, resembles lead III.

Group B (Twelve Cases).—Examples of this type are shown in charts 5, 9, 10 and 11 and in a previous publication (case 3).[2b] The characteristics of the group are defined under the heads of the various leads.

Lead I: This lead may be entirely normal. If a change in the RS-T interval occurs, it consists of a depression (six or twelve cases) This is usually small.

Lead II: This lead usually shows a Q wave and an elevation of the RS-T interval. The Q wave persists. The elevation of the RS-T interval usually gives way in a few days to a sharply inverted T wave.

Lead III: This lead usually shows the most characteristic changes. There is a deep Q wave (eleven cases) which persists. The twelfth case (case 23, chart 9 *B*) showed a small Q wave. The RS-T interval is usually elevated in the early stages. After a few days this elevation disappears, and a sharply inverted T wave develops. The negative T wave remains for some time.

Lead IV: This lead often shows no abnormal findings. If a deviation of the RS-T interval appears, it consists of an elevation. Four cases showed slight elevations of the RS-T interval. Three showed upright T waves and two showed absence of T waves. In all but two, the initial downward deflection of Q R S was present, although it was small in four. In the later stages, this lead tends to become normal. In one case (case 32, chart 11) leads IV and V showed an elevation of the RS-T interval, when only a suggestion of such a change was seen in leads II and III. This elevation was more pronounced when the anterior electrode was placed at the apex than when it was situated nearer the sternum.

Lead V: The general statements made about lead IV apply to lead V. It may be normal; any deviations of the RS-T interval are elevations. After the acute phase, the tracing tends to return to normal. However, elevations of the RS-T interval have been more frequent and more pronounced (chart 9) in this lead than in lead IV.

Lead VI: This lead usually resembles lead III, with an elevation of the RS-T interval and a Q wave. Usually, however, these are smaller than in lead III.

It is of interest to note that both in the recent and the old cases in group B, particularly the latter, leads II, III, IV, V and VI tend to resemble one another, with a Q wave and inverted T wave (chart 10).

In group A, the rate of disappearance of the deviations of the RS-T interval, and the completeness of their disappearance tend to parallel the rate and completeness of clinical recovery. In group B, on the

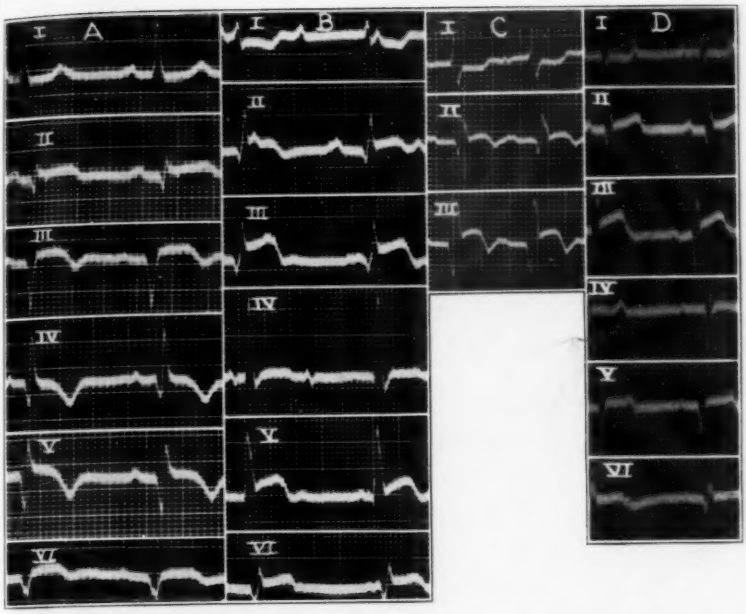

Chart 9.—Electrocardiograms of cases in group B. *A*, electrocardiograms of case 24 taken Oct. 4, 1932, with the anterior electrode in the fifth interspace, 4 cm. to the left of the sternum. Acute coronary occlusion occurred on September 26, eight days previously. Lead I is normal except for a slight suggestion of a depression of the RS-T interval. Lead II shows a Q wave and an elevation of the RS-T interval. Lead III shows a very pronounced Q wave, an elevation of the RS-T interval, and a beginning inversion of the T wave. Lead IV is practically normal. Lead V shows a slight elevation of the RS-T interval; otherwise it is normal. The initial downward deflection of Q R S in leads IV and V is preserved. Lead VI is a poor replica of lead III. Despite the deviations of the RS-T interval, this patient felt subjectively quite well at the time this tracing was taken. He walked into the hospital for the electrocardiogram.

B, electrocardiograms of case 23 taken on September 15, with the anterior electrode in the fifth interspace, 4 cm. to the left of the sternum. Acute coronary occlusion occurred on September 13. The patient had a complete heart block. (This disturbance of mechanism occurs in the experimental animal most commonly with occlusion of the left posterior circumflex artery, [1a] which supplies the posterior surface of the left ventricle.) Lead I shows a small depression of the RS-T interval. Lead II shows a Q wave and an elevation of the RS-T interval. Lead III shows Q wave and a marked elevation of the RS-T interval. Lead IV shows no definite elevation of the RS-T interval. Lead V shows a definite elevation of the RS-T interval. Lead VI is a poor replica of Lead III. The patient had a history of a previous attack of coronary occlusion. It seems likely, on account of the absence of the initial downward deflection of Q R S in leads IV and V, that this previous attack was an anterior infarction.

C and *D*, electrocardiograms of case 28, with the anterior electrode at the apex beat. Acute coronary occlusion occurred on Jan. 18, 1932. *C*, three leads taken January 19. Lead I shows a slight depression of the RS-T interval. Lead II shows a deep Q wave and an elevation of the RS-T interval. Lead III shows a Q wave and an elevation of the RS-T interval. *D*, taken on January 20. Lead I shows little. Lead II shows a Q wave and an elevation of the RS-T interval. Lead III shows a deep Q wave and a slightly greater elevation of the RS-T interval. Lead IV shows the persistence of the initial downward deflection of Q R S and an upright T wave. Lead V is similar but shows a slight elevation of the RS-T interval (slight elevations of RS-T in leads IV and V are probably more dependable for diagnostic purposes than slight depressions). Lead VI shows a Q wave and a slight elevation of the RS-T interval.

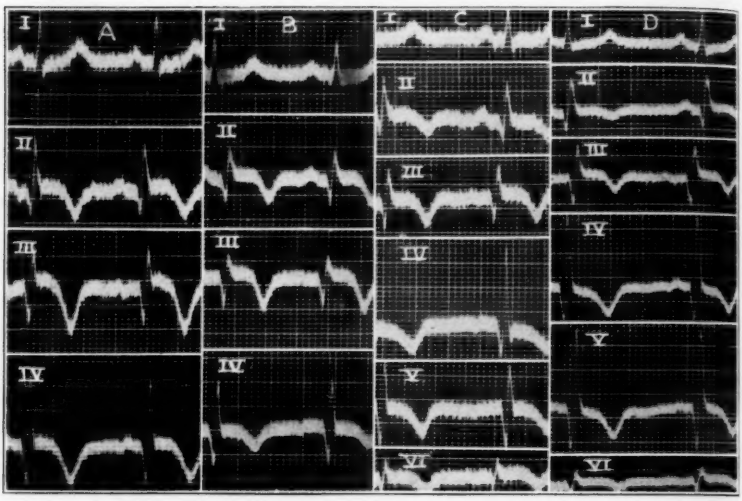

Chart 10.—Electrocardiograms of case 22, an example of group B, with the anterior electrode in the fifth interspace 4 cm. to the left of the sternum. Acute coronary occlusion occurred on Jan. 5, 1932, two days before the first tracing was taken.

A, four leads taken on January 7. Lead I shows nothing definite. Lead II shows a Q wave, slight elevation of the RS-T interval and a sharply inverted T wave. Lead III shows a deep Q wave, a definite elevation of the RS-T interval and a sharply inverted T wave. Lead IV is within normal limits. The initial downward deflection is preserved and the T wave is inverted. The presence of a prominent "shoulder" at the end of the RS-T interval in lead IV is suggestive of some abnormality. This patient had recovered considerably in two days and was able to walk into the hospital for the tracing.

B, four leads taken on February 9. The general characteristics of the previous tracings are preserved. The deviations of the RS-T interval are smaller, but still suggestive. The shoulder at the end of the RS-T interval in lead IV is less prominent.

C, six leads taken on March 15. There is not much change since December 9. Lead VI is a poor replica of lead III.

D, six leads taken on September 28, nine months after the attack. Slight elevations of the RS-T interval still persist in leads II, III and IV. Leads I, IV and V are normal. This is an example of the characteristic late findings in group B. Leads II, III, IV, V and VI are somewhat similar in that they possess initial downward deflections and inverted T waves.

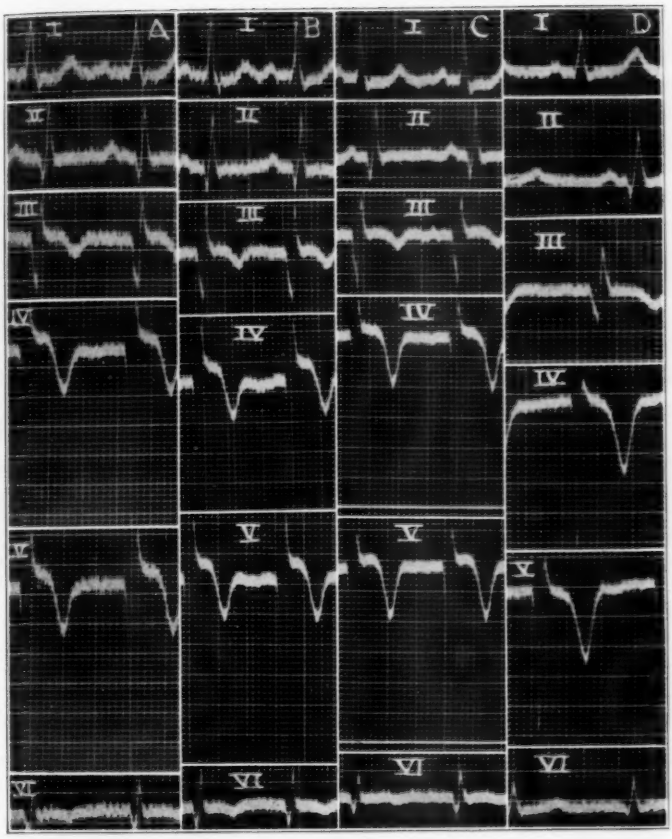

Chart 11.—Electrocardiograms of case 32, an example of group B. The anterior electrode was placed at the apex. Acute coronary occlusion occurred on December 5, 1932.

A, tracing taken December 8. There is a suggestion of a depression of the RS-T interval in lead I. Lead II shows a Q wave but no deviation of the RS-T interval. Lead III shows a deep Q wave, a slight elevation of the RS-T interval and an inverted T wave. Leads IV and V show a huge initial downward deflection of Q R S, an elevation of the RS-T interval of 3 mm. and a sharp deep T wave. Lead VI shows a Q wave. This is the only case in group B in which chest leads were essential to make the diagnosis of acute infarction.

B, tracing taken December 9, showing similar findings.

C, tracing taken December 12. The limb leads are much the same. The RS-T interval in leads IV and V has subsided considerably.

D, tracing taken, Jan. 6, 1933. Slight change has occurred in the limb leads. The elevations of the RS-T intervals in leads IV and V have disappeared, and the late findings of group B are evident.

Data on Cases *

Case	Color	Sex	Age	Date of Recent Occlusion	Date of Electrocardiogram	Group	Initial Downward Deflection of Q R S	RS-T Interval	T wave	Results and Comments
1. M. K.....	W	F	76	9/14/31	9/14/31	A	Previously reported,[2a] case 1			Sudden death 12/16/31
2. G. M.....	W	M	62	10/ 5/31	10/18/31	A	Previously reported,[2a] case 2			Sudden death 4/5/32
3. M. C.....	W	F	52	3/16/32	3/20/32 daily until 3/25/32	A	See chart 2			Sudden death 3/26/32; necropsy showed recent anterior infarction (see text)
4. D. G.....	W	M	42	10/22/32	10/25/32	A	See chart 3A			Death 10/26/32; necropsy showed recent anterior infarction (see text)
5. A. L.....	W	M	55	5/28/32	6/ 4/32	A	See chart 3B			Death 6/5/32; necropsy showed recent anterior infarction (see text)
6. S. S.....	W	M	51	7/21/32	7/25/32	A	See chart 8			Is able to do light work 1/4/33
7. W. E.....	W	M	52	7/14/32	7/21/32	A	Absent in I, II, III and IV; leads V and VI not taken	IV, −3 mm.	I, flat; IV, +5 mm.	Recovered; state of compensation moderately good 1/4/33
8. L. G.....	W	M	46	5/30/32	5/31/32 and daily after that for 10 days	A	Absent in all six leads	I, coveplane, no deviation; IV, −4 mm.; V, −3 mm.	I, sharply negative	
					6/ 2/32		Absent in all six leads	I, slight elevation; IV, −7 mm.; V, −6 mm. RS-T deviations in IV and V persisted until 6/7/32	.....	Activity markedly restricted; angina on effort
					11/ 7/32 (last tracing)		Absent in all six leads	No deviation	I, negative; IV and V, +2 mm.	
9. R. A.....	W	M	70	5/11/32	5/13/32	A	I, present; IV and V, absent	I, +1 mm.; IV, −4 mm.; V, −3 mm.	.....	Has marked restriction of activity; can walk 2 blocks (friction rub 5/12/32 at apex)
					10/30/32		Same	No deviation	I, negative; IV and V, +2 mm.	

10. T. D.....	W	M	60	11/ 7/32	11/12/32	A	I, present; IV and V, absent	I, no deviation; IV, −2.5 mm.; V and VI, not taken	I, negative; IV, markedly diphasic, −3 mm. and +4 mm.	Recovered sufficiently to return to work on a farm
					12/ 8/32	A	Same	IV, −1 mm.	IV, still diphasic; −1 mm. and +6 mm.	
11. H. H.....	W	M	62	12/ 6/31	12/16/31	A	I and IV, absent; V and VI, not taken	I, no deviation; IV, −2 mm.	I, negative; IV, +4 mm.	Died March, 1932; showed congestive failure throughout; digitalized at time of second tracing
					2/17/32		IV, returned slightly, −1.5 mm.	I, no deviation; IV, −1 mm.	I, flat; IV, +3 mm.	
12. M. G.....	W	M	56	11/10/32	11/10/32 3 hours after onset	A	—See chart 7—			Recovering slowly and inadequately 1/8/33
13. M. D.....	C	F	52	9/16/32	9/27/32	A	I, absent; IV and V, −0.5 mm.	I, no deviation; IV, −4 mm.; V, −3 mm.	I, flat	Died suddenly 9/28/32
14. M. B.....	W	M	62	2/27/32	3/ 6/32	A	I, present; IV and V, −0.5 mm.	I, +1 mm.; III, −0.5 mm.; IV, −3 mm.; V, −1 mm.	.....	Discharged 3/29/32 on the verge of congestive failure
					3/ 7/32		IV and V, absent	I and III, no deviation; IV, −3 mm.; V, −2 mm.		
					3/ 8/32		.....	I, +1 mm.; IV and V, −2 mm.		
					3/29/32		I, present; IV, −1 mm.; V, absent	No deviations	I, negative; IV and V, +5 mm.	
15. W. B.....	W	M	59	11/17/32	11/20/32	A	I, IV and V, absent	I, +1.5 mm.; II, +1 mm.; IV and V, −5 mm.	I, upright; IV and V, +2 mm.	Convalescing 12/2/32
16. J. K.....	W	M	41	10/ 5/32	10/14/32 repeated tracings until 11/8/32	A	I, IV and V, absent	I, no deviation; IV and V, −2 mm.	I, negative; IV and V, diphasic	Marked restriction of activity 11/8/32
							Same	No deviation	I, negative; IV, +4 mm.; V, +5 mm.	
17. N. F.....	W	M	53	10/23/32	10/29/32	A	I, IV and V, absent	I, curved upward; III, −1 mm.; IV and V, −3 mm.	.....	On the verge of congestive failure 11/26/32
					11/ 1/32		Same	I and III less deviation	I, negative	

* In order to conserve space in the table, the following abbreviations are used: The Roman numerals I to VI designate the leads. Following these numerals there are Arabic numerals with minus or plus signs preceding them. These signify the amplitude and direction of RS-T interval deviations from the iso-electric line. The amplitude and direction of T waves are indicated in a similar way.

Data on Cases—Continued

Case	Color	Sex	Age	Date of Recent Occlusion	Date of Electrocardiogram	Group	Initial Downward Deflection of Q R S	RS-T Interval	T wave	Results and Comments
17. N. F.....(Continued)					11/ 3/32		Same	I and III, no deviation; IV and V, −2 mm.	I, negative; IV and V, +4 mm.	
					11/ 9/32		Same	IV and V, −2 mm.	I, −2 mm.; IV and V, +8 mm.	
18. D. F.....	W	M	58	3/15/32	3/22/32	A	See chart 6			Not heard from since 4/29/32; marked restriction of activity
19. W. B. B...	W	M	54	12/22/32 12/28/32	12/24,27, 28/32	A	See chart 4			Died 12/30/32; full report in paper
20. P. S.....	W	M	56	1/12/32	1/13/32	Somewhat like A	Previously reported,[2b] case 1			Died in an attack of pulmonary edema 6/10/32; never recovered compensation
21. E. A. V...	W	M	63	9/19/32	9/20/32	Like A in I and III	I, small; IV and V, large	I, curved upward; III, suggestive depression; IV and V, no deviation	IV and V, −4 mm.	Died 10/26/32
				9/22/32	9/24/32	Like A in I and III	Same	I, +2 mm.; III, −2 mm.; IV and V, no deviation	Same	
22. R. S.....	W	M	43	1/ 5/32	1/ 7/32	B	See chart 10			Pain began in the back; back at regular work; recovered almost completely
23. W. W. R..	W	M	62	9/13/32	9/15/32	B	See chart 9B			Had had a previous attack of coronary occlusion; 12/15/32, activity markedly restricted
24. E. R.....	W	M	61	9/26/32	10/ 4/32	B	See chart 9A			Nine days after attack walked into hospital feeling quite well
25. M. L.....	W	F	63	2/17/32	2/28/32	B	Previously reported,[2b] case 3			Died with right hemiplegia (embolus?) 3/3/32
26. M. H.....	W	M	65	9/21/31	9/28/31	B	II, small; III, deep	III, curved upward; IV, +0.5 curved upward	.....	On 10/3/32 was working at dentistry on a slightly reduced schedule; good recovery

duced schedule; good recovery

27. E. M.....	W	F	57	12/27/31	12/28/31 (only limb leads)	B	II, absent; III, deep	I, −2 mm.; II, no deviation; III, +2 mm.	I, diphasic; III, upright	1/18/32, moderate restriction of activity
					12/29/31		IV and V, present	IV, no deviation; V, +1 mm.; VI, +0.5 mm.	IV, +1 mm.; V, +2 mm.	
					1/ 7/31		Same	No deviation	I, II and III, slightly inverted; IV and V, flat	
					1/18/31		III, IV and V, present			
28. M. K.....	W	M	50	1/18/32	1/19/32	B	——See chart 9C and D——			Died 1/25/32 from what was thought to be a mesenteric embolus
29. W. B.....	W	M	51	5/16/32	5/18/32	B	II, III and VI, deep; IV and V, small	I, −1 mm.; II, +2 mm.; III, +3 mm.; IV, +2 mm.	II and III, upright; IV and V, inverted	Discharged 6/28/32; says he feels just as well as before attack
					5/20/32		II, III and VI, deep; IV and V, −3 mm.	No deviations	II and III, upright	
					6/11/32		Deep in III, IV, V and VI	.....	Flat in all leads	
30. L. O.....	W	M	48	9/25/32	10/ 3/32	B	II, III, IV, V and VI, deep	I, slight depression; II and III, +1 mm.; IV and V, no depression	II and III, inverted; IV, diphasic; V, normal	Discharged 10/22/32; exercise tolerance moderately restricted
					10/30/32		Same	II and III, +1 mm.	II, III, IV, V and VI, inverted	
31. H. K.....	W	M	74	10/23/32	10/29/32	B	II, III, IV, V and VI, deep	II, curved upward; III and VI, +1.5 mm.; IV and V, no deviation	II, III, IV and VI, inverted	Effort angina on discharge 11/9/32
32. H. C.....	W	M	48	12/ 5/32	12/ 8/32	B	——See chart 11——			Convalescing satisfactorily 1/15/33
33. H. R.....	W	M	61	1/ 4/33	1/ 5/33	B	——See chart 5——			Full report in paper; died 1/8/33
34. J. S.....	W	M	67	6/ 7/32	6/12/32	(?)	——See chart 3C——			Died 6/16/32; full report in paper
35. A. H.....	W	F	51	4/12/32	4/12/32	B (?) findings indefinite	II and III, absent; IV and V, present	I, suggestion of slight depression, −1 mm.; III and VI, suggestion of slight elevation, +1 mm.; IV and V, normal	II and III, upright; IV and V, flat	Result unknown
36. L. S.....W....M....50				11/ 6/31	11/ 6/31	B (?)	——Previously reported,[3b] case 2——			Died suddenly, 11/6/31

other hand, although the extreme changes in the RS-T interval subside rapidly, slight deviations may persist for a long time in the face of what appears to be a fairly complete clinical recovery (case 22, chart 10).

In addition to these two main electrocardiographic groups, various other isolated types were seen. The electrocardiogram in case 20 resembled those in group A, but had little or no depression of the RS-T interval in leads IV and V and a marked elevation of this interval in leads I and II. The tracing in case 21 showed a high RS-T interval in lead I, a depression of this interval in lead III and no deviation in any of the other four leads. The electrocardiogram in case 36 resembled those in group B in certain respects, but was too bizarre to be considered a typical example.

Finally, the tracings in cases 34 and 35 showed no change in the RS-T interval in any lead. In case 34 (chart 3 *C*) there occurred a small infarction at the extreme apex of a heart which was the seat of previous extensive infarction. The tracing was not taken till six days after the attack. In the other case (35) the clinical diagnosis of coronary occlusion was fairly certain. The patient eventually recovered. A slight suggestion of elevation of the RS-T interval in lead III was the only pertinent electrocardiographic finding. Only one tracing was obtained for this patient, twelve hours after the onset.

Summary.—One might say that with a few exceptions our cases belong to one or the other of two electrocardiographic groups:

Group A consists of nineteen cases. The main electrocardiographic finding is a deep RS-T interval and a disappearance of the initial downward deflection in leads IV and V. This may or may not be accompanied by an elevation of the RS-T interval in lead I. The later findings are a subsidence of these deviations of the RS-T interval, the appearance of T waves of opposite sign and the continued absence of the initial downward deflection of Q R S in leads IV and V.

Group B consists of twelve cases. The main findings are a deep Q wave in lead III and an elevation of the RS-T interval, rapidly giving place to a sharply inverted T wave. Leads II and VI often show similar features. In leads IV and V the normal initial downward deflection of Q R S persists. If deviations of the RS-T interval appear in these two leads, they consist of elevations, not depressions. They are more common in lead V than in lead VI. They are occasionally seen in leads IV and V, when not clearly present in the limb leads, especially when the anterior electrode is situated at the apex (case 32, chart 11).

The electrocardiographic findings characteristic of group A probably indicate infarction of the anterior surface of the left ventricle, usually including the apex and the anterior portion of the interventricular septum, due to occlusion of the left anterior descending coronary artery.

The evidence for this statement may be summed up as follows: (*a*) The RS-T interval and T wave changes in the limb leads in group A are those which Barnes and Whitten [8] considered to be dependent on anterior infarction. (*b*) The deviations of the RS-T interval in the six leads resemble in general those seen in tracings of the dog after ligation of the left anterior descending coronary artery.[1] (*c*) Wilson and co-workers [9] stated that changes in the Q R S complex of this type are seen in patients who show anterior infarcts at necropsy. (*d*) Four of our cases in group A have come to necropsy and have shown recent anterior infarction (cases 3, 4, 5 and 19).

The electrocardiographic findings in group B probably indicate infarction of the posterior surface of the left ventricle resulting from occlusion of the right coronary artery. The following evidence supports this statement: (*a*) The changes in the RS-T interval and T wave in the limb leads in group B are those which Barnes and Whitten [8] considered to be dependent on posterior infarction. (*b*) The deviations of the RS-T interval in the six leads resemble in general those seen in tracings of the dog after ligating vessels supplying the posterior surface of the left ventricle.[1] (*c*) Fenichel and Kugell [10] and Wilson and his co-workers [9] stated that changes in the Q R S complex of the group B type are seen in patients showing posterior infarction at necropsy. Moreover, Wilson and co-workers [9] stated that "when there was an elevation of the S T segment in lead III, this occurred in the precordial leads also." (*d*) One case in group B came to necropsy, and showed a recent posterior infarction (case 33).

COMMENT

Chest leads have occasionally clinched the diagnosis in the cases in group B (case 32). However, their greatest usefulness seems to be in group A, since the deviations in the RS-T interval are almost always more pronounced and more persistent in leads IV and V than they are in the limb leads. It is our belief that most of the cases which have been electrocardiographically missed heretofore have probably been cases of anterior infarction.

The tracing gave evidence of acute coronary occlusion in the first examination of all but one of our patients for whom electrocardiograms

8. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, Am. Heart J. **5**:142 (Dec.) 1929.

9. Wilson, F. N.; Barker, P. S.; MacLeod, A. G., and Klostermyer, L. L.: The Electrocardiogram in Coronary Thrombosis, Proc. Soc. Exper. Biol. & Med. **29**:1006, 1932.

10. Fenichel, N. M., and Kugell, V. H.: The Large Q-Wave of the Electrocardiogram: A Correlation with Pathological Observations, Am. Heart J. **7**:235, 1931.

were made during the first five days. Thus the necessity for repeated tracings on successive days for diagnostic purposes is diminished by the use of chest leads in addition to limb leads. Nevertheless, we have seen patients (cases 19, 20 and 21) whose acute coronary occlusion was only suggested by the first tracing, whereas the tracing taken subsequently showed convincing evidence of the lesion. In all three of these patients the clinical findings suggested that the original infarct had been small. Moreover, subsequent symptoms pointed to an extension of the occlusion to other arteries between the taking of the first and the second tracings. However, it is not improbable that cases occur in which the area of anoxemia dependent on the occlusion of a certain vessel becomes temporarily enlarged. This might be due to (1) depression of the general circulation,[11] (2) temporary constriction of anastomosing coronary arteries, (3) reduction in pulmonary ventilation resulting from abdominal distention or (4) displacement of the heart in such a way as to impair coronary flow.[12] In such cases, without actual extension of the occlusion to other vessels, the lesion might at one time give no definite electrocardiographic findings, whereas at another time it might produce typical deviations of the RS-T interval.

Although no final analysis is possible at this time, it might be worth while to discuss the advisability of using each of the three chest leads. It is theoretically possible to multiply the number of chest leads ad infinitum with relatively little proportional increase in the information gained. A great deal of confusion could be produced by such a step. It seems to us, therefore, that the statement should be made that lead VI is often much like lead III, and that it has added nothing, so far, in the study of the patients in this series. However, its further use in cases of posterior infarction is necessary before it is entirely discarded.

Leads IV and V are undoubtedly useful. However, the question arises as to whether one of them could be discarded and only the other used. The evidence we have might be stated as follows: Leads IV and V are very similar for normal persons. For patients with heart disease without acute infarction these leads are also apt to be much alike. Nevertheless, for many patients with presumable anterior infarction, the

11. Feil, H. S.; Katz, L. N.; Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischaemia, Am. Heart J. **6**:522 (April) 1931.

12. This suggestion is based on the fact that when the experimental animal is placed in certain positions, the heart seems to twist on its pedicle of great vessels, and deviations of the RS-T interval appear. We have suspected that this was due to an angulation of one of the coronary arteries and a consequent impediment to the flow of blood through that vessel. It has seemed to us possible that this might occasionally occur in man. In fact, in certain patients with anginal pain, the assumption of the left lateral position seems to be a factor in the production of an attack.

depression of the RS-T interval is more marked in lead IV than in lead V (charts 6 and 8), and the contour of the T wave is often quite different in the two. On the other hand, in cases of supposed posterior infarction (chart 9*B*) there is often an elevation of the RS-T interval in lead V when none appears in lead IV. In our series of cases, one or the other of these two leads, in addition to the limb leads, would have sufficed to make the diagnosis. Nevertheless, we feel that it is reasonable to continue the use of both for the present.

Other chest leads, beside the three we have used as a routine, have not given additional information in any case thus far. However, when confronted with a patient in whom a recent coronary occlusion is suspected clinically, and for whom no diagnostic findings appear in the six leads, it would seem reasonable to attempt to bring out deviations of the RS-T interval by the use of other chest leads. Moving the anterior electrode to different points on the precordium should probably be the first procedure to consider.

Evidence is accumulating to show that it may be possible to locate the general position of an infarct in the heart by means of the electrocardiograph. Barnes and Whitten [8] have done the pioneer work in this field. Since their observations have been published, it has become evident that the electrocardiograph, as used in the past, is limited in its capacity to localize infarcts. In the first place, a certain group of cases have appeared in which no prediction of location has been possible because of the absence of localizing signs. In the second place, a small group of cases has been reported in which the location predicted from the electrocardiograph was proved wrong at necropsy.[13] By using chest leads, the first group of cases can probably be reduced in number. Further study is necessary before one can tell whether the second group will persist despite the use of chest leads.

From the standpoint of the localization of infarcts, the deviations in the RS-T interval seem to be of primary importance in the early stages of the disease. However, as Wilson and co-workers [9] pointed out, the significance of alterations in the Q R S complex must not be overlooked. In the first place they serve to corroborate the information derived from deviations in the RS-T interval in the acute stage. In the second place, they tend to persist, whereas the deviations of the RS-T interval are usually transitory. In group A (probably anterior infarction) the normal initial downward deflection of Q R S in leads IV and V was absent in fifteen of nineteen cases. In the other four this deflection was small, less than 2 mm. in amplitude. In only two of our cases in which this deflection was absent has it reappeared, despite the

13. Gilchrist, A. R., and Ritchie, W. T.: Ventricular Complexes in Myocardial Infarction and Fibrosis, Quart. J. Med. **23**:273, 1930.

fact that five of our patients have been followed for periods varying from three to seven months. In six cases a Q wave was present in lead I. In group B (probably posterior infarction) the initial downward deflection has tended to persist in leads IV and V, and a deep Q wave has been present in lead III in every case but one (case 23, chart 9 *B*). This wave also occurs in leads II and VI in most instances. Thus several months after a coronary occlusion the findings in the Q R S complexes and T waves may point to the nature of an antecedent attack. Chart 8 *C* illustrates the late findings in anterior infarction, and chart 10, those in presumable posterior infarction.

In three of our cases of acute coronary occlusion there were electrocardiographic evidences of previous infarction. In case 3 (chart 2) there was electrocardiographic and necropsy evidence of previous posterior infarction. Case 33 (chart 5) showed electrocardiographic and necropsy evidence of previous anterior infarction. Case 23 (chart 9 *B*) showed suggestions in the electrocardiograph of previous anterior infarction, but as necropsy was not performed this suspicion was not confirmed. Such findings may have a prognostic significance.

Before the subject of electrocardiographic localization of cardiac infarction is dismissed, it might be well to call attention to certain inherent limitations in the method which help to explain certain inconstancies in the findings of groups A and B:

1. The occlusion of a certain artery in the human heart cannot be expected to give the same electrocardiographic picture in every patient for the following reasons: (*a*) The type of electrocardiogram obtained probably depends on the relative positions of the heart, with its infarct, and the electrodes. Changes in the position of the heart in the experimental animal cause definite changes in the electrocardiographic features of a given infarct.[14] Therefore, when one considers the variable size, shape, axis and position of the human heart, it becomes obvious that an infarct in a certain location in the heart may vary in its electrocardiographic manifestations in minor ways. (*b*) The electrocardiographic characteristics of an acute infarct may be altered by changes in the Q R S complex caused by a previous infarction (case 3, chart 2, and case 33, chart 5). (*c*) The obstruction of a given coronary artery may produce ischemia of a much larger area than usual because of previous obstruction or occlusion of other coronary arteries. (*d*) The anatomic variation to which the coronary arteries are subject is another factor which may be responsible for unexpected electrocardiographic results.

2. The electrocardiographic findings in acute coronary occlusion are probably dependent on the exact size and location (with reference to the

14. Unpublished observations.

electrodes) of the ischemic area in the heart. One cannot determine with certainty at necropsy the exact size and shape of this area during life. It may have been much greater than the pathologic lesion and may have varied considerably from time to time, depending on the efficiency of (*a*) the general circulation, (*b*) the respiration and (*c*) the condition of the adjacent coronary circulation.

3. Marked deviations of the RS-T interval are probably produced by injured (living) muscle. When this injured muscle dies, the deviations of the RS-T interval probably disappear. If, therefore, the heart is the seat of a large infarct, in which the major portion of the involved heart muscle is dead, relatively small deviations of the RS-T interval might be recorded by the electrocardiograph (case 5). After a coronary occlusion has been present for several days, the obtainable deviations in the RS-T interval are probably produced by muscle situated at the periphery of the lesion, rather than by the main infarcted muscle mass. Therefore, unless one has obtained a tracing within a short time after the onset, one cannot say that the recorded deviations of the RS-T interval were caused by ischemic heart muscle located as the pathologic lesion is located. The main infarcted muscle mass may be dead and incapable of giving rise to deviations of the RS-T interval. For this reason, electrocardiographic studies of cardiac lesions produced with a cautery [15] must probably be interpreted with a certain degree of caution, especially if these lesions are large.

In the cases reported in this paper, there has been a difference in prognosis between the two groups, A and B. Of the nineteen patients in group A, eight have died of cardiac failure, eight are markedly restricted by their lesions, two have moderate restriction of activity, and one is almost as well as before the attack. Of the twelve cases in group B, four have made a practically complete recovery; three have slight restriction of activity, two are markedly restricted (one of these had a previous attack), and three have died, two probably as a result of embolus, not from cardiac failure. No definite opinion concerning prognosis should be formed until a large group is studied, and until more complete information is available as to localization. Nevertheless, it is coming to be our impression that the symptoms from a posterior infarction, when compared with an anterior one, are often less dramatic and less prolonged; that the immediate prognosis in the attack is less grave, and that subsequent recovery of adequate cardiac function is apt to be more rapid and more complete.

It has been the opinion of clinicians that occlusion of the left anterior descending artery is much more common than occlusion of any

15. Crawford, J. H.; Roberts, G. H.; Abramson, D. I., and Cardwell, G. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, Am. Heart J. **7**:627 (June) 1932.

other coronary artery. On the other hand, a recent pathologic study by Barnes and Ball [16] shows a somewhat similar incidence of anterior and posterior infarction. If, as suggested in the previous paragraph, there is really a clinical and prognostic difference between the two, the divergence of opinion, just referred to, might be explainable in one of two ways: 1. Clinicians may be right. Anterior infarction may be the more common. The greater frequency of death in the acute attack and the marked cardiac disability of the survivers may have tended to prevent patients with anterior infarction from reaching the institution where Barnes and Ball made their studies. Their series may therefore represent an involuntarily selected group. 2. Clinicians may be wrong. There may be a nearly equal incidence of anterior and posterior infarction. The erroneous belief that anterior infarction is the more frequent may have arisen as follows: Patients with this lesion are more profoundly ill and remain incapacitated for a longer time. Consequently, more of them consult the heart specialist or are admitted to the hospital, and are reported in the literature from these sources. On the other hand, the patients with posterior infarction are more often treated by the family physician at home, and make a smaller showing in the literature, except in studies of a group of consecutive unselected necropsies. It should be possible to decide on the merits of the first of these two explanations by pathologic studies from other sources, made in a way similar to those of Barnes and Ball.

We have occasionally encountered a patient with a presumable posterior infarction in whom the major part of the pain was located posteriorly and in the arms (case 22). Moreover, certain patients with anterior infarction have pain in the precordium and in the left upper quadrant of the abdomen. Thus far, however, the situation of the pain has not proved a reliable guide to the location of the infarct.

A reduction of blood pressure has usually been considered as one of the cardinal signs of acute coronary occlusion. However, in certain of our patients the blood pressure has been quite high for the first twelve hours, and a drop has not appeared until the next day. This phenomenon is probably well known to those who see a number of such patients, but it has not been sufficiently emphasized in the literature.

SUMMARY

Thirty-six cases of acute coronary occlusion are reported, in which chest leads as well as limb leads were used in the electrocardiographic study.

16. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215 (Feb.) 1932.

Three chest leads were used: lead IV, from the lower precordium to the angle of the left scapula; lead V, from the lower precordium to the left leg, and lead VI, from the angle of the left scapula to the left leg.

The exact location of the anterior chest electrode is important in determining the contour of the electrocardiogram. This has not been true in the case of the posterior electrode.

The methods used in taking chest leads and the normal findings in leads IV, V and VI are discussed.

Certain variations which have been seen in pathologic cases without acute cardiac infarction are described.

Deviations in the RS-T interval may occur in chest leads in the absence of acute coronary occlusion.

An electrocardiographic analysis of our thirty-six cases shows that thirty-one of them tend to fall in one or the other of two groups, termed for convenience groups A and B.

Group A consists of nineteen cases. Examples of this group are shown in charts 2, 3, 4, 6, 7 and 8. Four cases in this group which have come to necropsy have shown occlusion of the left anterior descending coronary artery, with infarction of the anterior surface of the left ventricle, usually including the apex and the anterior half of the interventricular septum.

Group B consists of twelve cases. Examples of this group are shown in charts 5, 9, 10 and 11. The data at hand suggest that these are cases of infarction of the posterior wall of the left ventricle due to occlusion of the right coronary artery.

When chest leads as well as limb leads were used, all but one of our cases of acute coronary occlusion showed electrocardiographic evidence of the lesion during the first few days. The absence of deviations of the RS-T interval in all six leads renders the diagnosis of recent coronary occlusion quite unlikely.

Certain characteristic alterations produced in the Q R S complex as a result of coronary occlusion tend to persist. Thus several months after a coronary occlusion has taken place the findings in the Q R S complexes and T waves may point to the nature of an antecedent attack.

There are certain indications that the symptoms of a posterior infarction, when compared with those of an anterior one, are often less dramatic and less prolonged; that the immediate prognosis is less grave, and that the subsequent recovery of adequate cardiac function is apt to be more rapid and more complete.

NOTE.—Since this article was submitted for publication there have been several further developments: The patient in case 8 died of acute cardiac failure on June 5, 1933. Necropsy showed an organized thrombus obstructing the left anterior descending coronary artery, 2 cm. from its

origin. There was a large fibrosed infarct in the anterior surface of the left ventricle, not involving the apex to any great extent. The anterior four fifths of the interventricular septum showed extensive endocardial scarring. The patient in case 15 died of cardiac failure in December, 1932. Permission for necropsy was not obtained. However, roentgenographic studies of the heart made prior to death by Dr. Ralph Bromer clearly showed an aneurysm protruding from the left border of the heart, in the region supplied by the left anterior descending coronary artery. Two other cases not published in this paper have come to necropsy. Their electrocardiograms showed the typical findings of group A. Pathologic examination showed occlusion of the left anterior descending coronary artery, with a large infarct in the anterior surface of the left ventricle in each case.

Thus the location of the infarct has been determined in eight cases in group A. In all eight the lesion has been situated in the interior surface of the left ventricle, in the distribution of the left anterior descending coronary artery.

A SIMPLE METHOD OF PRODUCING VASODILATATION IN THE LOWER EXTREMITIES

WITH REFERENCE TO ITS USEFULNESS IN STUDIES OF PERIPHERAL VASCULAR DISEASE

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Recent advances in the surgery of the sympathetic nervous system have made it increasingly necessary to develop a simple method for determining early in the course of peripheral vascular disease whether the diminished flow of blood to an extremity is due to simple arterial spasm or to obliterative structural disease of the blood vessels. The several tests now in use, though different in method, are similar in principle. The surface temperature of the distal portion of the cool, exposed extremity is measured thermo-electrically. Dilatation of the peripheral vessels is then produced, and the rise in surface temperature is recorded. The level to which the temperature rises with complete vasodilatation has been determined in persons with normal peripheral circulation. If the surface temperature fails to reach this normal level in a room at suitable temperature, the arteries supplying the part are regarded as being unable to dilate owing to organic changes in their walls.

We [1] observed that immersing the forearms and hands in warm water produced vasodilatation in the lower extremities. In ten observations made on the spontaneously cool lower extremities of six normal subjects the temperatures of the toes began to rise within fifteen minutes after the forearms were immersed in warm water. In all but one of these observations the surface temperature reached 32 C. (89.6 F.) within twenty-nine minutes after the forearms were immersed. In every instance the surface temperature exceeded 31.5 C. (88.7 F.), which

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From the Robinette Foundation of the Hospital of the University of Pennsylvania.

1. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**:1019, 1932.

Morton and Scott [2a] regarded as the minimum normal response to spinal and general anesthesia. It appears, therefore, that the vasodilatation induced by this procedure is comparable to the vasodilatation resulting from nerve block, general anesthesia or spinal anesthesia.

To produce vasodilatation by this relatively simple procedure requires no special apparatus and causes much less discomfort to the patient than the injection of typhoid vaccine or the induction of spinal or general anesthesia. We also described studies made on three patients who presented symptoms and signs of peripheral vascular disease. These studies illustrated the possible usefulness of this procedure in differentiating spasm from organic occlusion. The vasodilator response to warming the forearms and hands compared favorably with the vasodilatation produced in one patient by spinal anesthesia and in another by the intravenous injection of typhoid vaccine. The present paper describes the vasodilator response to warming the forearms and hands obtained in twenty-four patients with vascular disturbances involving the lower extremities. In eleven patients some other method of producing maximal vasodilatation was also employed, and the results have been compared with those obtained by immersing the forearms in warm water.

METHOD

Most of the observations were made on ambulatory patients who were seated with the legs extended so that the feet could rest comfortably on a stool about 15 inches (about 37 cm.) high. The room temperature was read from a mercury thermometer or a thermal junction suspended in the air near the toes. The feet and legs from a point just below the knees were exposed to the air of the room. The surface temperature of the toes was determined thermo-electrically, the thermal junctions being placed in contact with the skin on the dorsal surface of the distal phalanx just proximal to the base of the nail. In some instances the junctions were bare; in others a single layer of adhesive plaster covered the junction without modifying the results significantly. The skin temperature was read at intervals of two minutes while the exposed extremities cooled; when it had become sufficiently low, usually 26 C. (78.8 F.) or less, the forearms were immersed to the elbows in warm water the temperature of which was between 43 and 45 C. (between 109.4 and 113 F.). For this purpose ordinary white enameled arm baths, 52 cm. long, 20 cm. wide and 15 cm. deep, were entirely satisfactory. The temperature of the water was kept between 43 and 45 C. by means of a small electric heating coil placed beneath each bath. While the forearms were immersed the skin and room temperatures were read every minute.

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2. Morton, J. J., and Scott, W. J. M.: (*a*) Methods for Estimating the Degree of Sympathetic Vasoconstriction in Peripheral Vascular Diseases, New England J. Med. **204**:955, 1931; (*b*) The Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, J. A. M. A. **97**:1212 (Oct. 24) 1931; (*c*) Sympathetic Activity in Certain Diseases, Especially Those of the Peripheral Circulation, Arch. Int. Med. **48**:1065 (Dec.) 1931; (*d*) Some Angiospastic Syndromes in the Extremities, Ann. Surg. **94**:839, 1931.

Certain patients (cases 2, 9, 10, 13 and 20) were confined to bed. The head of the bed was elevated so that the patient assumed a semirecumbent position. The arm baths with the electric heating coils beneath them were placed on boards laid on the bed beside the patient. The forearms and hands could be completely immersed without discomfort. The lower extremities were exposed to the air and were examined in the usual way.

In normal subjects it was found that the skin temperature of the toes began to rise within fifteen minutes or less and reached 32 C. (89.6 F.) within twenty-nine minutes after the forearms were immersed in warm water. In the observations described in this article the forearms were immersed continuously for thirty-five minutes, a period definitely longer than that required for a complete vasodilator response in normal subjects. However, when the temperature of the toes reached 32 C. before the total period of thirty-five minutes had elapsed the observation was, in some cases (e. g., case 1, fig. 1) terminated, since the full normal response had been obtained and nothing was to be gained by prolonging the period of immersion. The color of the skin was estimated according to the scale devised by Lewis.[3a]

OBSERVATIONS

1. *Normal Vasodilator Responses in Patients with Pain, Coldness, or Cyanosis of the Lower Extremities.*—This group of patients all presented certain symptoms which are frequently associated with deficient circulation in the lower extremities; none of them had ulcers or gangrene. In some of these patients the cause of the pain, coldness or cyanosis was relatively clear, but this simple test proved useful in showing the diminished circulation could not be due to obliterative structural disease of the arteries, since the peripheral vessels were able to dilate normally

The normal vasodilator response observed in this group of patients is illustrated in figure 1, which shows the details of an observation on the patient in case 1, who suffered from varicose veins and chronic thrombophlebitis.

Case 1.—O'M., a white man, aged 52, was admitted to the University Hospital on April 23, 1932, with a chief complaint of "swelling of the legs." He had had varicose veins for many years, with painless swelling of the right ankle for four years. In October, 1931, he experienced a sudden, severe, dull pain in the calf of the right leg. The pain was continuous and was neither relieved nor made worse by movement or rest. In December, 1931, the same symptoms appeared in the left leg. In January, 1932, the right leg began to swell from below upward, and in March the left leg swelled also. The patient had observed blueness of the toes since February, 1932.

Physical examination showed edema of both legs and thighs, the right lower extremity being slightly larger throughout than the left. Both feet were mod-

3. Lewis, T.: (*a*) Standard Colours for Use in the Study of Vascular Reactions of Human Skin, Heart **15**:1, 1929; (*b*) Experiments Relating to Peripheral Mechanism Involved in Spasmodic Arrest of Circulation in the Fingers, a Variety of Raynaud's Disease, ibid. **15**:7, 1929.

erately cyanotic. Neither posterior tibial artery could be palpated. The pulsation of the left dorsalis pedis artery was felt, but the right was impalpable, owing probably to the greater edema on the right side. Roentgen examination of the feet revealed no evidence of arteriosclerosis, but numerous phlebolites were found on both sides. Venous pressure was measured indirectly by the capsular method of Krogh, Turner and Landis.[4] With the patient in the recumbent position, venous pressure amounted to 24 cm. of water in the right foot and to 17 cm. of water in the left.

The details of the vasodilator response are shown in table 1 and figure 1. The temperature of the toes, originally 26.4 C. (79.5 F.), fell gradually to 24 C. (75.2 F.) on exposure to the air of a room with a temperature varying between 18 and 19 C. (between 64.4 and

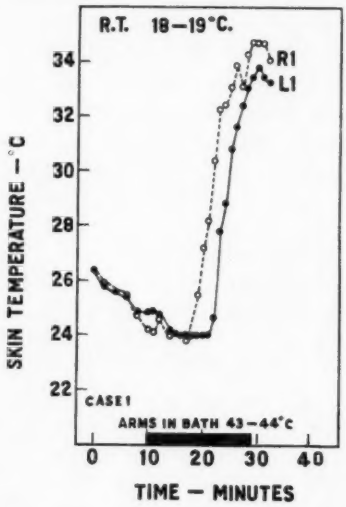

Fig. 1.—Normal vasodilator response observed in a patient (case 1) with bilateral thrombophlebitis. In this figure and in subsequent figures *L1* and *R1* indicate the skin temperature of the left and right great toes respectively; *R.T.*, the room temperature. The shaded area below indicates the period during which the forearms were immersed in warm water.

66.2 F.). At this time the color of the right and left great toes was X. Immersing the forearms in baths at a temperature of from 43 to 45 C. was followed by a feeling of warmth and, after five minutes, by perspiration first over the forehead and later over the entire body including the feet. Ten minutes after the forearms were immersed the color of the right great toe was VI, and that of the left great

4. Krogh, A.; Turner, A. H., and Landis, E. M.: A Celluloid Capsule for Measuring Venous Pressures, J. Clin. Investigation **11**:357, 1932.

TABLE 1.—*Normal Vasodilator Responses in Patients with Pain, Coldness or Cyanosis of the Lower Extremities*

Case	Sex	Age	Side	Diagnosis	Pain	Coldness	Cyanosis	Arterial Pulse: Posterior Tibial	Arterial Pulse: Dorsalis Pedis	Vasodilator Response: Room Temperature, C.	Vasodilator Response: Toes Observed	Vasodilator Response: Initial Temperature of Toes, C.	Vasodilator Response: Time From Immersion to Beginning of Rise, Minutes	Vasodilator Response: Time to Reach 32 C., Minutes	Vasodilator Response: Temperature at End of Period of Immersion, C.
1	M	52	R	Chronic thrombophlebitis, bilateral	+	++	+	Not palpable	Not palpable	19.0	R 1	24.1	9	13	**34.7**
											R 3	23.8	12	17	34.3
			L		+	++	+	Not palpable	Palpable		L 1	24.8	13	17	33.5
2*	F	25	R	Normal	None	None	None	Palpable	Palpable	22.0	R 1	29.1	5	6	36.3
			L	Old arterial embolism	+	None	+	Not palpable	Palpable (?)		L 1	24.9	10	16	34.3
											L 3	24.0	13	22	33.2
3	M	30	R	Congenital arteriovenous fistula, phlebitis	+++	None	+++	Palpable	Palpable	23.0	R 1	23.1	7	11	33.9
											R 3	23.2	7	14	33.8
			L	Normal	None	None	None	Palpable	Palpable		L 1	20.8	7	12	35.4
											L 3	20.6	7	14	34.5
4	M	51	R	Congenital arteriovenous fistula	None	None	++	Palpable	Palpable	11.5	R 2	19.0	5	15	32.2
			L	Normal	None	None	None	Palpable	Palpable		L 2	19.8	5	11	33.2
5	M	21	R	Sciatic neuritis	++	None	None	Palpable	Palpable (?)	24.0	R 1	26.7	8	11	34.3
											R 3	26.7	7	11	33.6
			L	Normal	None	None	None	Palpable	Palpable (?)		L 1	27.3	7	10	35.0
											L 3	26.9	7	11	33.7
6	M	44	R	Sciatic neuritis, traumatic	++++	++	+++	Palpable	Palpable	22.0	R 1	31.4	5	3	34.1
											R 3	31.1	5	4	33.5
			L	Normal	None	None	None	Palpable	Palpable		L 1	32.1	3	..	35.3
7	M	35	R	Atrophic arthritis, bilateral	++	+++	++	Palpable	Palpable	15.0	R 3	20.9	9	15	32.8
			L		++	+++	++	Palpable	Palpable		L 3	22.5	7	10	33.7

* This patient suffered from subacute bacterial endocarditis. The rectal temperature at the time of examination was 38.5 C. (101.3 F.).

toe, VII. The temperature of the right great toe began to rise definitely by the ninth minute after the immersion of the forearms; the left great toe began to warm by the thirteenth minute. The temperatures were both above 32 C. seventeen minutes after the forearms were immersed. The observation was terminated nineteen minutes after the forearms were immersed, since a completely normal response had been obtained.

The details of similar responses obtained in seven patients with various conditions are shown in table 1, which gives the sex, age and diagnosis for each patient and also the relative severity of the pain, coldness or cyanosis (graded from + to ++++). The details of the vasodilator responses are shown to the right. In any one observation the room temperature did not vary more than a degree above or below the average figure recorded. The initial temperature of the toes refers to the skin temperature at the time the forearms were immersed in warm water. Preceding this the lower extremities were exposed to the air of the room so that the toes might become cool before the vasodilator response was elicited. The column headed "Time from Immersion to Beginning of Rise" refers to the period elapsing between the time when the forearms were immersed and the time when the temperatures of the toes had risen 1 degree centigrade (1.8 degrees Fahrenheit) above the initial temperature. Elevations of temperature less than 0.5 C. (0.9 F.) were found to have little significance in normal subjects. When the skin temperature rose 1 C., however, the vasodilator response had always definitely started, and the skin temperature continued to rise more or less rapidly until the maximum was reached. The time required for the skin temperature to reach 32 C. is also shown to amplify data previously published. The skin temperature observed at the end of the period of immersion is recorded for comparison with data in tables 2 and 3.

The room temperature was usually kept between 19 and 24 C. (between 66.2 and 89.9 F.). It required from three to thirteen minutes necessary to lower it before the extremities began to cool. The fact that even then the skin temperature eventually rose above 32 C. is of interest, since it indicates that the complete vasodilator response can be obtained at low as well as at high environmental temperatures. When cold, the toes showed colors of the skin between VIII and XII (Lewis scale). Within from five to ten minutes after the forearms were immersed the patients felt warmer and began to perspire. The color of the skin at the tips of the toes rapidly changed to VI, or even V, when vasodilatation began. This was followed within a few minutes by the rise in temperature, though, as will be mentioned later, in the presence of organic obstruction the color of the skin may change without an increase in skin temperature.

The initial temperature of the toes varied between 19 and 32.1 C. (between 66.2 and 89.8 F.). It required from three to thirteen minutes for the skin temperature to rise 1 C. above the level observed at the time of immersion. In general, though not without exception, the time required for the rise to begin was shorter when the initial skin temperature was higher. The exceptions may have been due to slight grades of obstruction, which, though not great enough to make the response abnormally low, were sufficient to cause a slight delay (e. g., case 1, left). The figures for this group are, however, entirely within the range of variation previously observed in normal subjects. The toes all warmed to 32 C. usually within fifteen minutes after the forearms were immersed, but four of the twenty-one digits examined required from sixteen to twenty-two minutes to reach 32 C. The longest time observed in a normal subject was twenty-nine minutes. The maximum temperature reached during the period when the forearms were immersed varied between 32.2 and 35.8 C. (between 90 and 96.4 F.) in afebrile patients, while in one febrile patient (case 2) the highest skin temperature was 36.3 C. (97.3 F.).

The results obtained in this group of patients permit only one conclusion, namely, that the symptoms or signs present cannot be ascribed to organic narrowing of the arteries. In the patient in case 2 there was good reason to believe that an arterial embolism had caused the disappearance of the posterior tibial pulsation in the left foot, but in view of the normal vasodilator response it must be concluded that collateral circulation was adequate to maintain the nutrition of the tissues. In the absence of any evidence of structural disease of the arteries the cyanosis in the patients in cases 1, 3 and 4 was ascribed to the high venous pressure and the resultant engorgement of the subpapillary venous plexus to which the color of the skin is due. This elevated venous pressure was not sufficient, however, to prevent an adequate flow of blood to the tissues. The patients in cases 5 and 6 were Jewish and were of the age group in which thrombo-angiitis obliterans is a diagnostic possibility. The normal responses excluded organic obstruction. Case 7 illustrates the vascular spasm which frequently accompanies atrophic arthritis. In such varied conditions, therefore, as thrombophlebitis, sciatic neuritis, arteriovenous fistula and arthritis, the reactions to warming were such that the cyanosis, coldness and pain could not be ascribed to a diminished flow of blood due to obliterative structural disease of the arteries.

2. *Vasodilator Responses in Patients with Thrombo-Angiitis Obliterans.*—The vasodilator response to immersing the forearms in warm water was tested in five patients with thrombo-angiitis obliterans, as illustrated in figures 2 (case 8) and 3 (case 10).

Case 8.[5]—Ga., a white woman of Jewish ancestory, aged 31, had been suffering for the past three years from coldness and blueness of the right foot, with intermittent claudication and cramps in the right leg. Typical migratory phlebitis had occurred in the right leg during the first year after the onset of the symptoms. The toes of the right foot were habitually cold. Except for some coldness of the foot she had experienced no symptoms in the left extremity. The patient used tobacco excessively in the form of cigarets. A right femoral periarterial sympathectomy performed in October, 1931, had produced no symptomatic improvement.

Physical examination in March, 1932, yielded no findings of importance except those in the lower extremities. Both feet were cold to the instep. At first the toes of the right foot were conspicuously blanched, while those of the left foot

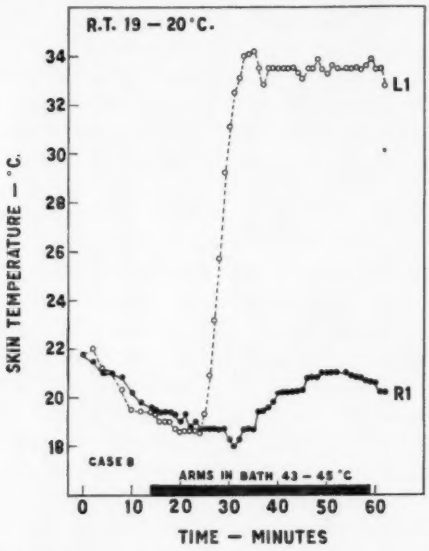

Fig. 2.—Vasodilator response in a patient with thrombo-angiitis obliterans (case 8). The skin temperature rose normally on the left but only slightly on the right.

were normal in color. The patient was seated with the feet supported about 15 inches from the floor. The color gradually returned to the right foot, and cyanosis, which was at first slight (color X½), became complete (color XIV) in the course of ten minutes. The color of the left foot was normal in the dependent position. Pulsation was felt in the dorsalis pedis and posterior tibial arteries of both feet.

Thermal junctions were fixed to the dorsal surfaces of the distal phalanges of the right first and second toes and the left first toe. As is shown in figure 2, the skin temperature on both sides, originally 22 C. (71.6 F.), gradually fell during twenty minutes to room temperature, which was between 19 and 20 C. (between

5. Dr. Alfred Stengel permitted us to report this case and Dr. Lee Rademaker supplied determinations of the vasomotor index.

66.2 and 68 F.). The forearms were then immersed in water baths maintained at a temperature of from 43 to 45 C. Five minutes later the patient felt warm and began to perspire. The skin temperature of the left great toe began to rise twelve minutes after the immersion of the arms and reached a maximum of 34.2 C. (93.5 F.)—a normal reaction. Simultaneously the color of the right foot brightened, finally becoming pink (colors V to VI). The surface temperatures of the right toes began definitely to rise twenty and thirty-two minutes after immersion of the arms and reached maxima of 21 C. (69.8 F.) for the right first toe and 23 C. (73.4 F.) for the right second toe—a conspicuously abnormal reaction. In this test the forearms were immersed for forty-five minutes. It can be seen in figure 2 that no further rise in temperature occurred during the last ten minutes of the period of immersion.

The history and physical findings were typical of thrombo-angiitis obliterans. The response to immersion of the arms in hot water showed a high grade of

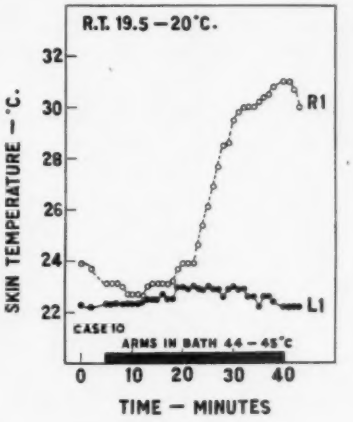

Fig. 3.—Vasodilator response in a patient in an advanced stage of thrombo-angiitis obliterans (case 10). The response was practically absent in the left foot and was only partial in the right foot.

organic occlusion in the vessels of the right leg. The coldness of the opposite leg was necessarily ascribed to spasm in view of the normal rise in temperature obtained when vasodilatation was induced. These findings agree with the vasomotor index determined in this patient by Dr. Lee Rademaker some months earlier. The index for the right foot was 2.5, and that for the left was 3.3, indicating that the symptoms on the right side were due largely to organic occlusion, while the coldness of the left foot was due to simple spasm.

Figure 3 shows the results of the same procedure in a patient with more advanced thrombo-angiitis obliterans.

CASE 10.—Ju., an Italian man, aged 33, was admitted to the University Hospital in April, 1932, complaining of pain in the left foot. During December, 1931, the sole and dorsum of the left foot had become constantly painful, with exacerbations in cold weather and after activity. At times the patient experienced in the

right calf the constricting type of pain characteristic of intermittent claudication. The left foot was occasionally edematous. The right foot and calf were sometimes slightly painful.

Positive physical findings were limited to the extremities. The feet were cold, and the skin was thickened. Elevating the feet produced blanching, which, after the legs were again dependent, persisted longer in the left foot. When the left leg was dependent the toes became deeply purple, the cyanosis extending well over the instep. The right foot was only slightly cyanotic. The right dorsalis pedis could be felt clearly. The left dorsalis pedis and both posterior tibial arteries were not palpable.

As is shown in figure 3, immersing the forearms in warm water induced vasodilatation in the right foot, but the rise in temperature was delayed (beginning after eighteen minutes) and partial, since the great toe warmed only to 31 C. (87.8 F.), while, as is shown in table 2, the temperature of the second toe reached only 24.7 C. (76.4 F.). No response could be detected in the left toes. It appeared, therefore, that the blood vessels of the left leg were conspicuously involved by organic changes, while those of the right were only slightly involved. A test of the vasomotor index yielded values of 1.3 for the right toes and 0 for the left.

The vasodilator responses observed in five patients with thromboangiitis obliterans are summarized in table 2. In two cases (8 and 12) the skin temperature rose above 32 C. in one extremity while showing no change or only a partial rise in the other extremity. As is usually the case, both extremities cooled equally when exposed to the air, but when vasodilatation was induced the diminished flow of blood in the more seriously affected extremity was seen to be due to organic obstruction, whereas in the other extremity the vessels, while tending to go into spasm, were still capable of dilating. In the other three cases (9, 10 and 11) the absent or partial vasodilator response indicated organic obstruction to the flow of blood in both extremities.

In three patients (cases 8, 9 and 11) the vasodilator response to warming the forearms was tested more than once. It may be seen in table 2 that the results obtained in the same patient are qualitatively similar, although the initial temperature of the toes and that of the room were sometimes different. On two occasions the patient in case 9 showed no response in either lower extremity. On three occasions the patient in case 8 showed a complete or an almost complete absence of response in the right foot and an entirely normal response in the left foot. On two occasions the patient in case 11 showed no response in the right foot and only a partial response in the left foot. Accurate quantitative comparisons are impossible unless the successive observations are carried out at a constant room temperature. However, in spite of unavoidable seasonal variations in environmental temperature, the results of repeated observations showed good qualitative agreement.

3. *Vasodilator Responses in Patients Showing Arteriosclerosis.*—Patients with arteriosclerosis have been grouped into two categories:

TABLE 2.—*Vasodilator Responses in Patients with Thrombo-Angiitis Obliterans*

Case	Sex	Age	Date of Examination	Side	Pain	Coldness	Cyanosis	Ulcers or Gangrene	Arterial Pulse: Posterior Tibial	Arterial Pulse: Dorsalis Pedis	Vasodilator Response: Room Temperature, C.	Toes Observed	Initial Temperature of Toes, C.	Time From Immersion to Beginning of Rise, Minutes	Time to Reach 32 C., Minutes	Temperature at End of Period of Immersion, C.
8	F	31	March, 1932	R	+++	+++	++++	None	Palpable	Very faintly palpable	19.2	R 1	19.6	32	..	20.6
												R 2	19.0	20	..	21.8
				L	None	++	None	None	Palpable	Palpable		L 1	19.4	12	17	33.9
			April, 1932	..	.....	.....	.....	.....	.....	.....	20.0	R 1	19.6	..	..	18.5
												R 3	18.9	..	..	18.0
												L 1	19.5	20	28	34.2
												L 3	18.8	21	29	33.6
			June, 1932	..	.....	.....	.....	.....	.....	....	25.7	R 1	25.9	18	..	27.6
												R 3	25.7	24	..	27.2
												L 1	25.9	6	13	34.0
												L 3	25.8	10	15	31.7
9	M	26	Feb. 1932	R	+++	+++	++	Gangrene	Not palpable	Not palpable	17.0	R 3	22.9	..	..	22.2
												R 4	23.0	..	..	23.4
				L	++	+++	++	Gangrene	Not palpable	Not palpable		L 3	21.8	..	..	20.6
												L 4	20.8	..	..	20.0
			March, 1932	..	.....	.....	.....	.....	.....	.....	20.0	R 2	25.0	..	..	24.0
												R 3	26.2	..	..	25.4
												L 2	25.4	..	..	24.6
												L 3	25.8	..	..	24.6
10	M	33	April, 1932	R	+	+++	+	None	Palpable	Palpable	20.0	R 1	23.1	18	..	31.0
												R 2	21.6	23	..	24.7
				L	++++	+++	++++	None	Palpable	Not palpable		L 1	22.3	..	..	22.2
												L 2	22.2	..	..	21.6
11	M	58	June, 1932	R	+++	+++	++++	None	Not palpable	Not palpable	25.7	R 1	27.1	..	..	27.4
										Palpable		L 1	27.4	8	..	31.4
				L	None	+++	None	None	Not palpable	.....	18.8	R 1	23.6	..	..	22.5
			March, 1933	..	.....	.....	.....	.....	.....	.....		R 3	24.4	..	..	24.1
												R 5	23.5	..	..	23.2
												L 1	23.5	21	..	25.6
												L 3	23.4	18	..	25.0
12	M	34	June, 1932	R	++	++	+++	None	Not palpable	Not palpable	27.2	R 1	29.2	13	..	30.5
												R 3	28.5	8	..	30.5
				L	None	None	None	None	Not palpable	Palpable		L 1	29.7	5	8	33.9
												L 3	28.7	7	12	32.5

(*a*) those without diabetes and (*b*) those with diabetes. Figure 4 illustrates the findings in the patient in case 13 whose symptoms were ascribed to simple arteriosclerosis.

CASE 13.—Za., a Jewish man, aged 53, was admitted to the University Hospital in June, 1932, complaining of pain in the left leg. He had been well until 1930, when, according to his statement, he suffered a "stroke," with paralysis of the right leg and left arm. Practically complete power had returned to the affected extremities by the time he was admitted to the hospital. During January, 1932, he experienced pain in the left leg while walking. The pain came on gradually, disappeared with rest and reappeared on further exertion. It was always confined to the left leg and ankle. At this time the right leg had never been painful. During a period of four weeks before admission the pain had become worse. He had used cigarets excessively for many years but had recently reduced the number to ten or less per day.

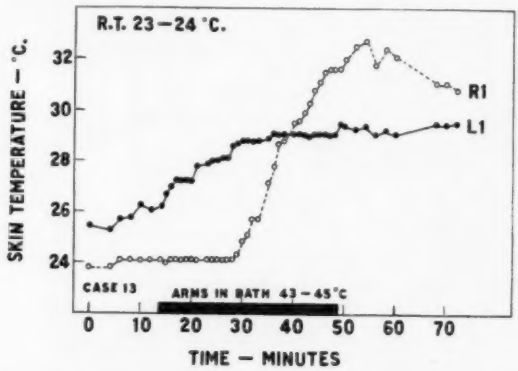

Fig. 4.—Vasodilator response in a patient with arteriosclerosis (case 13). The response was partial in the left foot and was much delayed in the right foot.

On examination the patient had a blood pressure of 165 systolic and 80 diastolic. The heart was slightly enlarged to the left, and a systolic apical murmur was present. Both lower extremities were cold at a room temperature of 24 C. The dorsalis pedis artery was felt on the right side but not on the left. Neither posterior tibial artery was palpable. The right foot was pale but showed no trophic changes. The left toes, however, were moderately cyanotic (color X). Under the nail of the great toe the skin was tender and extremely cyanotic (color XIV). The skin of the left toes was dry, thick and fissured. Roentgen examination showed calcification of the vessels of both legs.

The vasodilator response in the left leg, as shown in figure 4, was incomplete, reaching a maximum of 29.5 C. (85.1 F.). The right toes warmed very slowly, the first toe finally reaching a temperature of 32 C., though not within the thirty-five minute period of immersion. This indicated that the vessels of both lower extremities were organically diseased, though those of the left leg were more severely affected.

Table 3*a* summarizes the findings in five additional cases of arteriosclerosis. With one exception (patient 17) both extremities were affected. In patient 13, although the temperature of the right great toe finally reached 32 C., it did so only after the abnormally long period of thirty-six minutes. Frequently, also, the rise in temperature began at a later time than normal. It is noteworthy that the most pronounced diminution in response was usually found in patients with ulcers.

The complete absence of a vasodilator response in a patient with arteriosclerosis, diabetes and gangrene is illustrated in figure 5 (case 21).

CASE 21.—Bl., an Irishman, aged 46, was admitted to the University Hospital in January, 1932, suffering from diabetes mellitus with gangrene involving the toes of the right foot. One year before admission the patient had been treated elsewhere for an infected callus on the left foot. In November, 1931, the right foot became swollen, red and tender, and the diagnosis of diabetes mellitus was

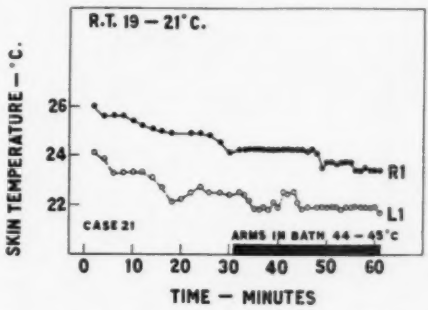

Fig. 5.—Chart showing complete absence of vasodilator response in a patient with advanced diabetic arteriosclerosis with gangrene (case 21).

made in another hospital. In spite of dietary treatment and the use of insulin, it became necessary to amputate the second toe of the right foot. At this time there was clinical evidence that the circulation was also deficient in the third and fourth toes of the right foot.

At the time of the patient's admission to the University Hospital the temperature, pulse and respiration were normal. The blood pressure was 130 systolic and 75 diastolic. The peripheral arteries, as well as the retinal vessels, were moderately sclerosed. The tips of the third and fourth toes of the right foot presented small areas of gangrene. A few drops of purulent exudate could be expressed from the site of the previous amputation. The pulsation of the dorsalis pedis artery was felt in both feet; the posterior tibial artery was not felt on either side.

On admission the blood sugar during fasting was 189 mg. per hundred cubic centimeters, and glycosuria occurred only occasionally. Roentgen examination of the right foot revealed marked osteoporosis of the bones of the anterior part of the foot and some calcification of the arteries.

In the hospital the diabetes was controlled easily by a suitable dietary regimen with the administration of 10 units of insulin per day. The lesions of the right foot improved temporarily under conservative treatment by débridement, antiseptics and external heat.

TABLE 3.—*Vasodilator Responses in Patients with Arteriosclerosis With and Without Diabetes*

Case	Sex	Age	Side	Pain	Coldness	Cyanosis	Ulcers or Gangrene	Arterial Pulse		Vasodilator Response				
								Posterior Tibial	Dorsalis Pedis	Room Temperature, C.	Toes Observed	Initial Temperature of Toes, C.	Time From Immersion to Beginning of Rise, Minutes	Time to Reach 32 C., Minutes	Temperature at End of Period of Immersion, C.
(a) Patients without Diabetes															
13	M	53	R	+	+	None	None	Not palpable	Palpable	24.0	R 1	24.1	17	..	31.8
											R 3	24.0	18	..	29.4
			L	++	++	++++	None	Not palpable	Not palpable		L 1	26.2	6	..	29.5
											L 3	24.9	18	..	27.1
14	M	58	R	++++	++++	+++	Ulcer	Not palpable	Not palpable	18.5	R 1	22.9	..	..	23.1
											R 3	22.3	..	..	22.3
			L	None	None	None	None	Not palpable	Not palpable		L 1	23.3	7	..	26.9
											L 3	23.0	10	..	25.4
15*	M	71	R	None	.....	.....	None	Not palpable	Not palpable	21.0	R 1	23.8	16	..	29.6
			L	+++	.....	.....	Ulcer	Not palpable	Not palpable		L 1	26.2	15	..	27.9
16*	M	63	R	++	+++	.....	Ulcer	Not palpable	Not palpable	16.0	R 1	19.6	25	..	21.2
											R 3	18.8	25	..	20.6
			L	++	None	.....	None	Not palpable	Not palpable		L 1	17.5	17	..	30.5
											L 3	17.5	19	..	25.6
17	M	58	R	+++	+++	++++	Ulcers	Palpable	Faintly palpable	23.5	R 1	26.5	..	..	25.5
											R 3	25.6	..	..	24.7
			L	None	+++	None	None	Palpable	Faintly palpable		L 1	26.9	9	15	35.0
											L 3	25.6	9	21	34.7

18	M	59	R	+++	+++	None	None	Not palpable	Not palpable	20.2	R 1	21.8	..	..	21.8
											R 3	21.5	..	..	21.4
											R 5	22.0	..	..	21.7
			L	++	+++	None	None	Not palpable	Not palpable		L 1	21.7	..	..	21.1
											L 3	21.7	..	..	21.4
							(b) Patients with Diabetes								
19	F	24	R	None	++++	None	None	Palpable	Faintly palpable	23.5	R 1	27.1	9	11	35.7
											R 3	26.2	9	13	34.9
			L	None	++++	None	None	Palpable	Palpable		L 1	25.6	11	28	34.1
											L 3	24.8	12	29	34.3
20	M	56	R	None	+++	+++	None	Palpable	Not palpable	20.0	R 1	19.2	..	..	19.9
											R 2	19.2	..	..	19.8
			L	None	+++	++	None	Palpable	Palpable		L 1	19.0	..	..	19.3
											L 2	19.2	..	..	19.8
										20.0	R 1	21.9	..	..	21.2
											R 3	22.4	..	..	21.3
											R 5	22.9	..	..	21.7
											L 1	21.6	..	..	20.8
											L 3	20.8	..	..	20.2
21	M	46	R	+++	++	+++	Gangrene	Not palpable	Faintly palpable	17.0	R 1	27.2	..	..	24.3
											R 4	26.8	..	..	24.9
			L	None	++	+++	Threatened gangrene	Not palpable	Palpable		L 1	25.1	..	..	21.9
											L 4	22.3	..	..	21.0
										20.5	R 1	24.2	..	..	23.4
											R 4	24.2	..	..	23.4
											L 1	22.6	..	..	21.7
											L 4	22.5	..	..	21.9

* Colored patient.

On two occasions the skin temperature of the toes of both feet was measured while the forearms were immersed in warm water. The results were entirely similar, though in one instance the examination was made at a room temperature of 17 C. (62.6 F.), and in the other at 20.5 C. (68.9 F.). When the feet were exposed to the air the temperature of the toes fell slowly but constantly. Immersion of the forearms in warm water had no effect on the temperature of the toes, although subjective warmth and sweating occurred within eight minutes after warming the arms. These findings indicated the presence of a high grade of organic obstruction to circulation in the toes of both feet.

In table 3 *b* the results obtained in this patient and in two others with diabetes are summarized. One of these (case 19) was a young woman, aged 24, who had severe diabetes and who suffered only from

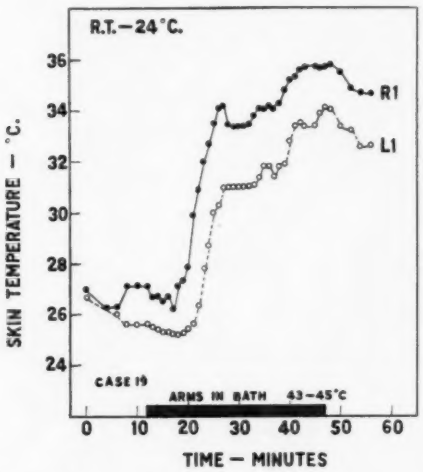

Fig. 6.—Vasodilator response in a diabetic patient (case 19) with mild symptoms of diminished circulation in the lower extremities. The response was normal in both lower extremities, indicating that the symptoms were due to vasospasm, not to organic occlusion.

coldness of the extremities without other evidence of restricted flow of blood. She had a practically normal vasodilator response (fig. 6). The other two patients (cases 20 and 21) had more severe vascular involvement with clinical evidence of organic obstruction; they showed no vasodilator response in the lower extremities when the forearms were immersed in warm water.

4. *Comparison with Other Methods of Producing Maximal Vasodilatation.*—Evidence has already been reported by us[1] to show that in normal subjects adequate warming of the forearms causes the skin temperature of the toes to rise above 31.5 C. (88.7 F.), the figure

adopted by Morton and Scott as the minimal normal response to general and spinal anesthesia. In eight of the thirteen patients with thromboangiitis obliterans or arteriosclerosis in whom the temperature of the toes failed to rise to the normal level on warming the forearms, some other method of producing vasodilatation was also employed.

The vasomotor index [6] was determined in four patients (cases 8, 9, 10 and 11) with essential agreement between the two methods used. In patient 8 the vessels of the left foot were able to dilate fully and the vasomotor index was 3.3, while in the right foot, the vessels of which failed to show normal dilatation to heat, the vasomotor index was 2.5. In patient 9 the vasomotor index for both lower extremities was zero, and the vessels failed also to show measurable dilatation when the forearms were warmed. Warming the forearms of patient 10 produced practically no vasodilator response on the left side; the vasomotor index was zero. A partial response was produced on the right side; the vasomotor index was 1.5. Patient 11 showed almost no response to warming in the right foot; the vasomotor index was 1.3. There was a much delayed response in the left foot, with a vasomotor index of 1.1. In these four patients the agreement between the vasodilator response due to warming the forearms and that due to fever was good. It is difficult to compare quantitatively methods which differ as much as these two, but the clinical interpretation of the findings was essentially the same in each case.

One patient (case 14) was studied by means of both spinal anesthesia and warming the forearms. The clinical record and the details of both examinations have been given in full by us.[1] The two methods of inducing dilatation were carried out at the same room temperature, and the final skin temperatures were almost identical.

Anesthetization of the posterior tibial nerve was used in three patients who showed no vasodilator response to warming the forearms. In patient 18, at a room temperature of 20 C. (68 F.), both feet were cold, the temperatures ranging from 21.5 to 22.6 C. (from 70.7 to 72.7 F.). Immersion of both forearms in warm water (43 to 45 C.) for thirty-five minutes produced no rise in the temperature of the toes. The heating was adequate since the patient felt uncomfortably warm and perspired profusely during the test (table 3). Ten days later, at a similar room temperature 3 cc. of a 2 per cent solution of procaine hydrochloride was injected around the right posterior tibial nerve. The right first and fourth toes, the temperatures of which were originally 20 and 20.7 C. (68 and 69.3 F.), became warmer as anesthesia appeared, and nineteen minutes after anesthesia was complete

6. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, J. A. M. A. **87**:379 (Aug. 7) 1926.

the temperatures were 27.1 and 29.7 C. (80.8 and 85.4 F.) respectively. The rise in temperature was slow and incomplete, indicating a moderate grade of organic obstruction to the flow of blood. Had it been assumed in this case that complete absence of the vasodilator response to immersing the forearms in warm water was always due entirely to organic obstruction, it would have been concluded erroneously that a very high grade of obstruction was present, whereas anesthetization of the posterior tibial nerve showed that the organic obliteration was only moderate.

In two other cases the vasodilator response to heat was absent and anesthetization of the posterior tibial nerve under similar environmental conditions likewise failed to produce any rise in skin temperature. One patient (case 21) suffered from diabetes with gangrene, and the vasodilator response to warming the forearms was not obtained in two examinations at room temperatures of 17 and 20.5 C. (table 3). At a room temperature of 18 C., the injection of 3 cc. of a 2 per cent solution of procaine hydrochloride near the left posterior tibial nerve failed to produce any rise of temperature in the area of anesthesia, though the color of the skin improved slightly. The other patient (case 20) on two occasions, at a room temperature of 20 C., showed no vasodilator response to warming the forearms. Likewise, at a room temperature of 19 C., anesthetizing the right posterior tibial nerve with procaine hydrochloride failed to produce any rise in skin temperature.

Therefore, in seven of eight patients with organic vascular obstruction the results obtained by testing the reaction to warming the forearms agreed with those obtained by other methods of examination. In one patient the vasodilator response to heat failed to appear, although the vessels were shown by anesthetization of the posterior tibial nerve to be capable of limited dilatation.

5. *The Vasodilator Response in Acrocyanosis.*—According to Lewis and Landis,[7] the essential vascular abnormality in acrocyanosis appears to consist of heightened tone in the arterioles of the skin of the affected part at ordinary environmental temperatures. The vasodilator response to warming the forearms was tested in three patients with typical acrocyanosis involving the lower extremities. These patients had no local symptoms other than coldness of the extremities and occasional tingling in the digits. They had not suffered from ulcers, phlebitis or trophic changes.

On examination the pulsation of the posterior tibial and the dorsalis pedis arteries was felt in all these patients. The feet and hands, which

7. Lewis, T., and Landis, E. M.: Observations upon the Vascular Mechanism in Acrocyanosis, Heart **15**:229, 1930.

were rather more deeply red than normally when warm, cooled rapidly and became cyanotic when exposed to an air temperature of about 20 C. The discoloration was not uniform, being deeper blue in some areas, particularly over the knuckles, and more reddish in other areas. The cyanosis involved all the digits, extending in the hands to a point slightly above the wrist, and in the feet to the ankles, though it was less intense in the more proximal areas of skin. In two patients cyanosis was noted in the legs above the ankle.

The cyanosis disappeared when the extremities became warm spontaneously or as a result of immersion in warm water. With the

TABLE 4.—*Vasodilator Responses in Patients with Acrocyanosis of the Lower Extremities*

Case	Sex	Age	Room Temperature, C.	Side	Toes Observed	Initial Temperature of Toes, C.	Vasodilator Response to Warming the Forearms	Vasodilator Response to Anesthetization of the Posterior Tibial Nerve
22	M	38	19-20	R	R 1	23.1	None	Normal
					R 2	22.1	None	Normal
				L	L 1	23.4	Normal	.....
					L 2	23.2	Normal	.....
23	M	14	19-20	R	R 1	19.9	Partial and delayed	Normal
					R 3	19.8	None	Normal
				L	L 1	20.0	Partial and delayed	.....
					L 3	19.6	Partial and delayed	.....
24	M	19	18-20	R	R 1	20.4	None	.....
					R 3	20.3	None	.....
				L	L 1	20.6	None	Normal
					L 3	19.6	None	Normal

change in tint the depth of color lessened. The introduction of histamine by needle prick into the cyanotic skin released vascular spasm more or less completely in the area of flare which, in some instances, appeared brilliantly hyperemic in contrast to the adjacent cyanotic skin. Wheals appeared at the usual time around the points of puncture.

Table 4 summarizes the changes in digital temperature in the lower extremities obtained by immersing the forearms in warm water and by blocking the posterior tibial nerve with a 2 per cent solution of procaine hydrochloride. Each patient was first tested in the usual manner, the forearms and hands being immersed for thirty-five minutes in water at a temperature of between 43 and 45 C. The patients felt warm and perspired freely over the face and body during the test. Nevertheless, the skin temperature of the toes failed to rise in the normal manner, the response being absent in the more involved foot of one patient, incomplete in both feet of the second patient and totally

absent in both feet of the third patient. Anesthetization of the posterior tibial nerve, however, produced vasodilatation, and the skin temperature rose eventually to 32 C. or higher in each instance, indicating that the vessels were capable of complete normal dilatation.

In figure 7 a comparison is made of the effects on skin temperature in the toes of warming the forearms and anesthetization of the posterior tibial nerve. The feet of the patient (case 24) cooled to room temperature and were deeply cyanotic (colors XII and XIII½). On the twenty-fourth minute the forearms were immersed in warm water, but the feet failed to show the usual rise in temperature. On the seventy-fourth minute the thermal junction applied to the skin of the

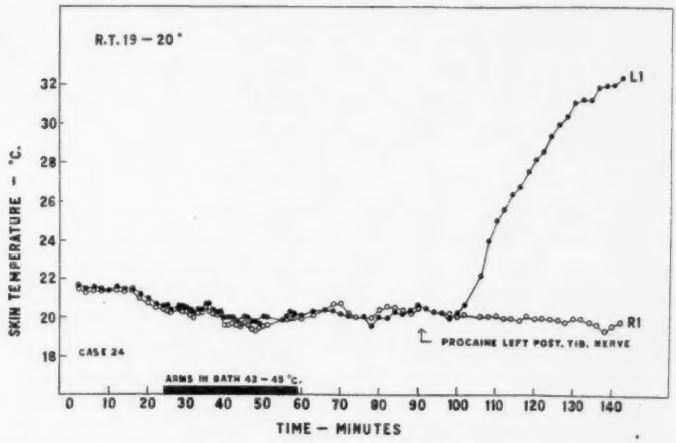

Fig. 7.—Chart showing complete absence of vasodilator response in a patient with acrocyanosis of the lower extremities (case 24) when the forearms were immersed in warm water. Injection of procaine hydrochloride around the left posterior tibial nerve produced vasodilatation and a rise in skin temperature.

left great toe was moved from the dorsal to the plantar surface to correspond with the procedure of Scott and Morton.[2b] On the ninety-first minute 3.5 cc. of a 2 per cent solution of procaine hydrochloride was injected in the region of the left posterior tibial nerve. Partial anesthesia appeared eleven minutes later, and nineteen minutes after the injection anesthesia was complete in the area of the nerve. It required forty minutes for the skin temperature to rise from 20 C. to 32 C., and during the last thirty minutes of this period the plantar skin of the left foot was completely anesthetic. The color of the anesthetic skin changed for the most part to a deep pink (colors VI to VII), but some areas on the plantar surfaces of the toes remained

blue (colors XII and XIII). A similar delayed, but eventually complete, response to anesthetization of the posterior tibial nerve was observed in patient 23.

COMMENT

The practical importance of differentiating the deficient circulation due to vasospasm from that due to organic occlusion of the arteries has been stressed sufficiently by Brown [7] and by Scott and Morton.[2c] The usefulness of sympathetic ganglionectomy in the treatment of patients with obliterative structural disease of the arteries, as indicated by Scott and Morton and by Adson and Brown,[8] is greatest in patients with only mild grades of organic obstruction. The best results in the treatment of peripheral vascular disease can be obtained only if the beginning organic occlusion is discovered before it has reduced too greatly the ability of the blood vessels to dilate when vasoconstrictor tone is abolished permanently by sympathetic ganglionectomy. Since early diagnosis of beginning organic occlusion will be favored by any simplification of the existing methods of examination, it was considered worth while to determine whether the vasodilator response described previously by us could be applied to the clinical study of peripheral vascular disease. Heat has been used also by Lewis and Pickering [9] and by de Takats,[10] but special apparatus is required in the methods employed by them, the body being warmed in an electric cabinet in the former case and by means of diathermy apparatus in the latter.

Vasodilatation can be produced simultaneously in both upper or in both lower limbs by immersing the other two extremities in warm water. This method is simple and requires no special apparatus except that for measuring skin temperature. The test can be performed without serious discomfort or danger to the patient, whether he is ambulatory or confined to his bed. Studies were made to determine whether this form of vasodilator response was sufficiently dependable to be recommended as a preliminary method of examination since, by reason of its simplicity, the procedure may be used by practitioners who are not equipped to apply methods such as nerve block, spinal or general anesthesia and diathermy.

The vasodilator response elicited in the lower extremities by immersing the forearms in warm water appears to be sufficiently trustworthy to use as a preliminary test of organic occlusion. In seven of eight patients

8. Adson, A. W., and Brown, G. E.: Thrombo-Angiitis Obliterans: Results of Sympathectomy, J. A. M. A. **99**:529 (Aug. 13) 1932.

9. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, Heart **16**:33, 1931.

10. de Takats, G.: The Differentiation of Organic and Spastic Vascular Occlusions, Ann. Surg. **94**:321, 1931.

with thrombo-angiitis obliterans or arteriosclerosis tested by this and one other method the clinical conclusions arrived at by the two procedures were practically identical. The one exception was a patient with roentgen evidence of arteriosclerosis in the lower extremities in whom the vasodilator response to heat was completely absent while anesthetization of the posterior tibial nerve showed only a moderate grade of organic occlusion. It may be concluded that significant organic occlusion is certainly absent if the immersion of the forearms in warm water (43 to 45 C.) for thirty-five minutes causes the skin temperature of the toes to rise to 31.5 C. or more. A partial response with a rise of skin temperature in a room at 20 C. to a level below 31.5 C. indicates organic obstruction, the grade of the obstruction being roughly measured by the difference between 31.5 C. and the maximum level reached. Until more comparative studies have been made it would seem advisable to verify the conclusions based on such partial responses with some other method of examination. The test has proved extremely valuable in ruling out significant organic vascular defects in patients with mild or atypical symptoms which hardly justified the use of intravenous typhoid vaccine or of spinal or general anesthesia as a diagnostic procedure.

There are two conditions, Raynaud's disease and acrocyanosis, in which peripheral vasoconstriction due to central vasomotor tone is more or less increased by local spasm of peripheral vessels which are hypersensitive to cold. Raynaud's disease, while it may be purely a vasomotor neurosis in its earlier stages (Simpson, Brown and Adson [11]) is often complicated in later stages by local sensitivity of the digital and palmar arteries to cold (Lewis,[3b] Simpson, Brown and Adson,[11] and Morton and Scott [2b,d]). In acrocyanosis the diminished flow of blood is due apparently to spasm of the cutaneous arterioles, which are abnormally sensitive to cold (Lewis and Landis [6]). It is conceivable that the peripheral vascular spasm in these two conditions might prove more difficult to relax on account of the local factor which is present only rarely in thrombo-angiitis obliterans and in arteriosclerosis.

We have not had the opportunity of studying the vasodilator responses in patients showing Raynaud's malady in the lower extremities. Morton and Scott,[2b, d] however, observed that in some cases of Raynaud's disease, while anesthetization of the posterior tibial nerve eventually relaxes spasm in the anesthetic area, the vasodilatation is slowly progressive. Some degree of impairment in the local circulation may be noted for a considerable time after complete anesthesia is established.

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11. Simpson, S. L.; Brown, G. E., and Adson, A. W.: Raynaud's Disease; Evidence That It Is a Type of Vasomotor Neurosis, Arch. Neurol. & Psychiat. **26**:687 (Oct.) 1931.

Three patients with typical acrocyanosis failed to show normal vasodilator responses during warming of the forearms. When histamine was pricked into the skin the cyanosis disappeared more or less completely in a small area corresponding to the usual flare. In these patients anesthetization of the posterior tibial nerve produced dilatation, with a concomitant increase in skin temperature to levels well above 30.5 C (86.9 F.). In the patient in whom the condition was mildest the temperature rose to the level characteristic of complete vasodilatation in a relatively short time. In the other two patients, in whom the condition was more severe, a longer time was required for the anesthesia to modify skin temperature and skin color. According to Scott and Morton,[2b] the maximum skin temperature is reached within from fifteen to thirty minutes after complete anesthesia is obtained, so that the delay in these patients can hardly be regarded as definitely abnormal.

Lewis and Pickering[9] found that warming the body in a chamber equipped with electric lamps as sources of heat produced dilatation of the vessels in the hands of patients with Raynaud's disease and acrocyanosis. This response "once initiated is rapid and of the normal type." Immersing the forearms in warm water may possibly be a slightly less adequate stimulus for producing vasodilatation in the lower extremities. Moreover, it is well known that vasoconstrictor tone is greater in the lower extremities than in the upper. Nevertheless, in earlier studies it was found that immersing the forearms in warm water at from 43 to 45 C. for thirty-five minutes produced complete vasodilatation in normal subjects at room temperatures of 11 and 16 C. (51.8 and 60.8 F.). The same procedure failed to produce complete vasodilatation in patients with acrocyanosis at room temperatures between 18 and 20 C. (between 64.4 and 68 F.). This difference is possibly due to the local sensitivity of the cutaneous arterioles to cold, rendering complete vasodilatation more difficult to obtain. Anesthesia of the appropriate mixed nerve apparently removes the spasm by primary relaxation of the deeper vessels in the arteriovenous anastomoses of the digits, the cutaneous arterioles themselves relaxing after they have become warm (Lewis and Landis[6]).

The anomalous results which may be obtained by warming the forearms of patients with Raynaud's disease and acrocyanosis will only rarely be confusing. The history and ordinary examination usually suffice to differentiate these vasospastic conditions from the more common peripheral vascular diseases such as thrombo-angiitis obliterans and arteriosclerosis in which it is important that the grade of organic occlusion be determined. Finally, if in a preliminary study the vasodilator response to warming the forearms is abnormal and if doubt exists with respect to the diagnosis, another method of producing vasodilatation should be used for comparison.

SUMMARY

1. The forearms of patients were immersed in warm water (43 to 45 C.) for thirty-five minutes in order to produce vasodilatation in the lower extremities. This vasodilator response was studied in twenty-four patients who showed clinical evidence of peripheral vascular disease.

2. In seven patients with pain, coldness or cyanosis of the lower extremities the temperature of the toes rose to levels above 32 C. This normal response definitely excluded the possibility of obliterative structural disease of the arteries as a cause of the diminished flow of blood in the lower extremities.

3. Fourteen patients with thrombo-angiitis obliterans or arteriosclerosis involving the lower extremities showed varying grades of organic occlusion and spasm when tested by this method.

4. In eight of the thirteen patients who failed to show the normal vasodilator response to warming the forearms the results were compared with those obtained by some other method of producing vasodilatation, including the intravenous injection of typhoid vaccine, the use of spinal anesthesia and anesthetization of the posterior tibial nerve. In seven of the eight patients the clinical interpretation of the findings by both methods was the same. In one patient with arteriosclerosis warming the forearms failed to produce a vasodilator response, whereas anesthetization of the posterior tibial nerve showed that the vessels were capable of limited dilatation.

5. Three patients with acrocyanosis of the lower extremities showed abnormal vasodilator responses to warming the forearms, though anesthetization of the posterior tibial nerve produced complete, but rather delayed, elevations in skin temperature. These findings are discussed with reference to the mechanism of the diminished flow of blood in acrocyanosis.

6. Warming the forearms in water at a temperature of from 43 to 45 C. for thirty-five minutes is a simple and entirely unobjectionable method of producing vasodilatation in the lower extremities. If the surface temperature of the toes rises above 31.5 C., significant obliterative structural disease of the arteries of the lower extremity is definitely absent. If the surface temperature fails to rise to this level, organic arterial obstruction is probably present. With controlled room temperature, the approximate grade of the organic obstruction is indicated by the difference between 31.5 C. and the maximum temperature reached. For absolute certainty in the diagnosis of organic arterial obstruction the abnormal vasodilator responses obtained by warming the forearms should be confirmed by some other method of producing peripheral vasodilatation.

EFFECT OF ALKALI ON THE ABSORPTION OF THYROXINE FROM THE GASTRO-INTESTINAL TRACT

WITH A NOTE ON THE COMPARATIVE EFFECTS OF SYNTHETIC AND "NATURAL" THYROXINE INJECTED INTRAVENOUSLY

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We have just reported observations which show that when thyroxine is administered by mouth in the form of its monosodium salt to patients with myxedema it has only about from one-third to one-fifth as much effect as when it is administered intravenously in alkaline solution (sodium hydroxide).[1] This conclusion was based on the amounts of the two substances which had to be administered every day in order to hold the basal metabolism at the normal level. Pure thyroxine had much less effect than its monosodium salt. Since when thyroxine is dissolved in an excess of sodium hydroxide the disodium salt is presumably formed, it seemed logical to try the effect of administering the hormone by mouth in an alkaline solution.

Klein[2] reported that Hoffmann-La Roche thyroxine solution for oral use, Schering thyroxine in alkaline solution with the same p_H as

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1. Thompson, W. O.; Thompson, P. K., and Dickie, L. F. N.: Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine: Comparison of Their Effects When Administered Orally with the Effect of Thyroxine Injected Intravenously in an Alkaline Solution, Arch. Int. Med. **52**:576 (Oct.) 1933.

2. Klein, B.: Ueber die hohe Wirksamkeit peroral verabreichten Thyroxinnatriums bei normalen und hypothyreotischen Individuen, Ztschr. f. klin. Med. **119**:477, 1932.

the Hoffmann-La Roche solution and Schering's *Trinktabletten* all have a greater effect on the basal metabolism than the tablets which the Schering Corporation ordinarily sells for oral use. The two solutions and the *Trinktabletten* are said to contain dialkali salts of thyroxine, whereas the Schering tablets commonly sold for oral administration presumably contain the monosodium salt of thyroxine. Baur and Loewe [3] stated that an alkaline solution is more effective than tablets (presumably monosodium salt), especially if the alkaline solution is markedly diluted. The data on this point are very meager, and we know of no observations in which the effects of administering thyroxine in alkaline solution by the oral and parenteral routes have been compared in the same patient.

METHOD

In this study we have used as a basis of comparison the effect of a single dose of the substance concerned on the basal metabolism. Only patients with definite myxedema were used because in them the effect of thyroxine on the basal metabolism is greater than in normal persons. There were three such patients. In the first and second the myxedema was spontaneous, and in the third it followed a subtotal thyroidectomy for exophthalmic goiter.

For all intravenous injections the thyroxine was prepared by dissolving it in a few cubic centimeters of distilled water by the addition of from 1 to 3 drops of 10 per cent sodium hydroxide. The solution was sterilized on a water bath for the first patient and for the second injection in the second patient. For the other injections it was sterilized by the addition of 1 cc. of 1:1,000 merthiolate [4] to make a dilution of 1:5,000. For oral administration of an alkaline solution the method varied slightly, as described in the legends. Sodium bicarbonate was always administered with the alkaline solution. All thyroxine administered by mouth was synthetic thyroxine (Hoffmann-La Roche) or one of its sodium salts. The monosodium salt was administered in the form of tablets prepared by Hoffmann-La Roche, each of which contained 1.03 mg. of the salt, or the equivalent of 1 mg. of pure thyroxine.

Basal metabolic rates were determined by means of the Sanborn-Benedict apparatus, with the Aub-DuBois standards.

The data on the second patient up to the forty-second day and those on the third patient up to the one hundred and forty-fourth day have been reported elsewhere to illustrate another point.[5]

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3. Baur, H., and Loewe, G.: Ueber die Wirkung des synthetischen Thyroxins beim Menschen mit normaler Schilddrüse, Deutsches Arch f. klin. Med. **159**:275, 1928.

4. One gram of sodium ethylmercuri-thiosalicylate in 1,000 cc. of water buffered with 1.4 Gm. of sodium borate in 1,000 cc. and containing sodium chloride to make the solution approximately isotonic. This preparation was supplied by the manufacturers, Eli Lilly and Company, Indianapolis.

5. Thompson, W. O.; Alper, J. M.; Thompson, P. K., and Dickie, L. F. N.: The Effect of Diiodotyrosine on the Basal Metabolism in Myxedema, to be published in the Journal of Clinical Investigation, January, 1934.

DATA

The data are recorded in charts 1 to 6 and summarized in the table.

The excess basal calories produced by the various doses of thyroxine were calculated as in a previous communication by Thompson, Thompson, Brailey and Cohen.[6] The daily metabolic rates were plotted on graph paper (charts 4 to 6) ruled in small squares (sample insert in each chart), each small square representing a change of 1 per cent in the normal basal calories per square meter for twenty-four hours. A curve was then plotted to denote the course of the metabolism. The base line was the level of the metabolism before the administration of

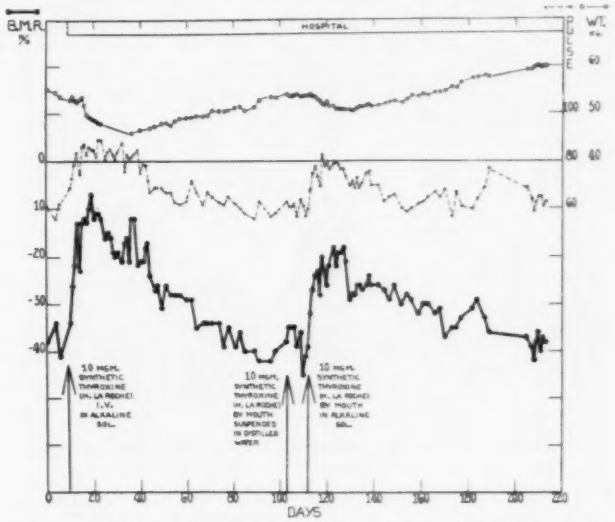

Chart 1.—Comparison of effects of an alkaline solution of thyroxine administered orally and intravenously and of pure thyroxine administered by mouth in a patient with myxedema (Mrs. M. M., height 159 cm., age 58). Intravenous injection at 10:10 p. m., Oct. 8, 1932. The oral dose of pure thyroxine was administered without breakfast or lunch at 12:30 p. m., Jan. 10, 1933, suspended in distilled water, a total of 200 cc. being used, largely for rinsing. The oral dose of thyroxine in alkaline solution was given without breakfast at 10:31 a. m., January 19, 2 drops of 10 per cent sodium hydroxide, and a total of 100 cc. distilled water being used for solution and rinsing. A total of 70 grains of sodium bicarbonate and 350 cc. of distilled water was also administered in six doses from 10:30 a. m. to 11:30 a. m., a single dose of 15 grains being given just before the thyroxine. In this and subsequent charts, the arrows denote the time of administration of thyroxine and *I.V.*, an intravenous injection.

6. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenetic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, J. Clin. Investigation **7**:437, 1929.

thyroxine. The number of squares contained in the area bounded by the base line and the curve was counted. The difference in the number of squares in the graphs for the various methods of administering thyroxine gives a fairly close estimate of the difference in the magnitude of the response to each: but to bring each response to terms of total excess heat production, the normal basal metabolic rate in calories for twenty-four hours was multiplied by the number of squares and the result divided by one hundred. In each calculation the figure used for surface area is that of the patient just before the administration of thyroxine. The ensuing changes in area are not taken into account

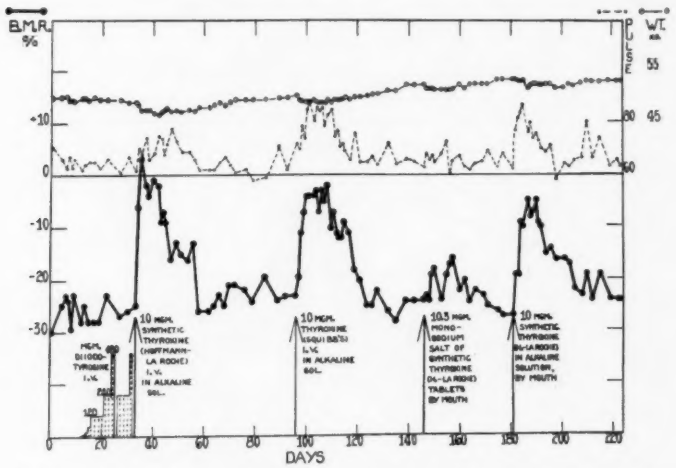

Chart 2.—Comparison of effects of administering an alkaline solution of thyroxine orally and intravenously and monosodium thyroxine by mouth in a patient with myxedema (Mrs. M. K., height 152 cm., age 36). The effects of administering synthetic and natural (Squibb's) thyroxine intravenously are also compared. The intravenous injection of synthetic thyroxine was made about 11:30 a. m., Aug. 8, 1932 (without breakfast), and the intravenous injection of the Squibb's thyroxine at 4:30 p. m., October 10. The monosodium salt was administered with about 100 cc. distilled water at 3:30 p. m., November 29 (she had had dinner at 12:15 p. m.). The thyroxine in alkaline solution (30 cc., with 3 drops of 10 per cent sodium hydroxide) was administered at 3:53 p. m., Jan. 3, 1933, after a mid-day dinner. A total of 50 grains of sodium bicarbonate with 165 cc. of distilled water was also given in five equal doses, from 3:51 to 5:15 p. m., the first dose being given just before the administration of the thyroxine.

because the influence on final results is so slight. As pointed out in the communication referred to, this method of calculating excess calories

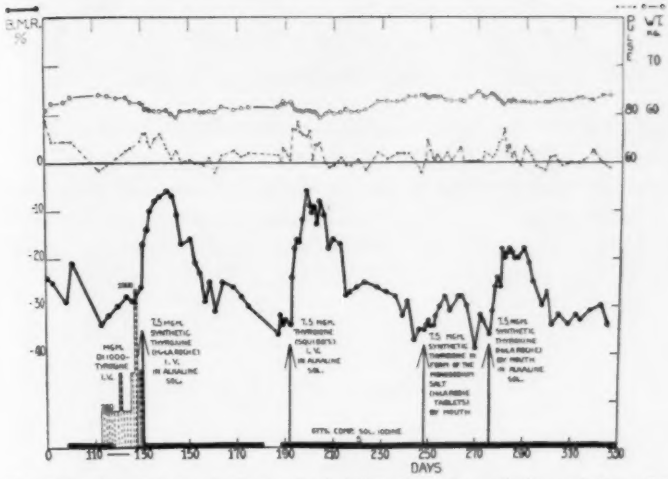

Chart 3.—Comparison of effects of administration of an alkaline solution of thyroxine orally and intravenously and monosodium thyroxine by mouth, and a comparison of the effects of administering synthetic and natural thyroxine intravenously, in a patient with myxedema (Mrs. A. R., height 160 cm., age 33). The intravenous injection of synthetic thyroxine was made about 11 : 30 a. m., Aug. 16, 1932, and the intravenous injection of natural (Squibb's) thyroxine at 3 : 30 p. m., October 17, after lunch. The monosodium thyroxine was given, without breakfast, at 11 : 30 a. m., December 12, with about 125 cc. of distilled water. The oral administration of synthetic thyroxine in alkaline solution (30 cc., with 4 drops of 10 per cent sodium hydroxide) was made at 2 : 48 p. m., Jan. 9, 1933 (the patient did not have breakfast or lunch). In addition, 60 grains of sodium bicarbonate was administered with 160 cc. distilled water in six equal doses, from 2 : 47 p. m. to 4 : 15 p. m., only one dose being given before the thyroxine. The solid black area represents the administration of compound solution of iodine.

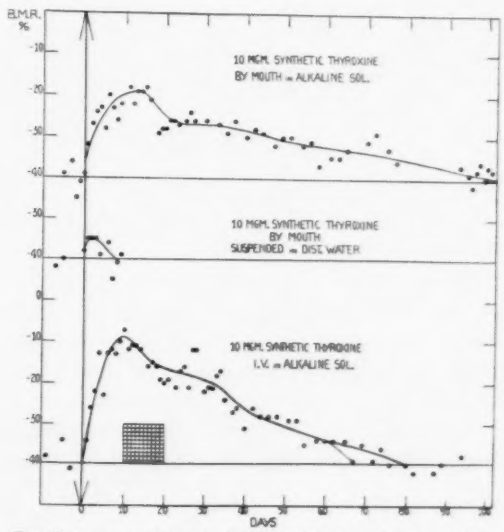

Chart 4.—Detailed comparison of effects on basal metabolism of various administrations of 10 mg. of thyroxine in the first patient.

is only a rough one because the number of calories produced above the basal value undoubtedly varies with different metabolic levels.

It may be seen that thyroxine in alkaline solution had from 68 to 80 per cent as much effect by mouth as by intravenous injection in terms of the amount of increase in the metabolism, and about 72 to 84 per cent as much effect in terms of total excess calory production. It may

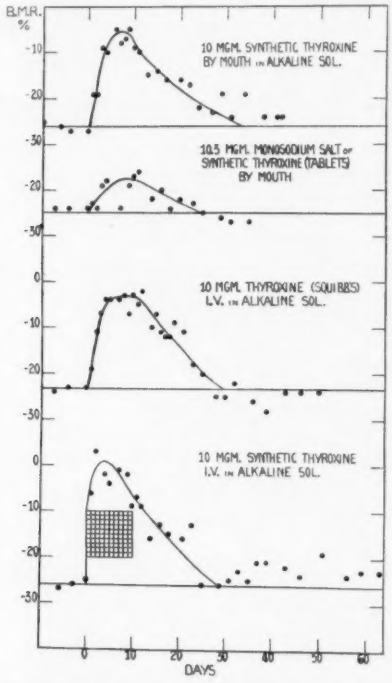
B.M.R. %
10 MGM. SYNTHETIC THYROXINE BY MOUTH IN ALKALINE SOL.
10.3 MGM. MONOSODIUM SALT OF SYNTHETIC THYROXINE (TABLETS) BY MOUTH
10 MGM. THYROXINE (SQUIBBS) I.V. IN ALKALINE SOL.
10 MGM. SYNTHETIC THYROXINE I.V. IN ALKALINE SOL.
DAYS

Chart 5.—Detailed comparison of effects on basal metabolism of various administrations of 10 mg. of thyroxine in the second patient. The 10.3 mg. of monosodium thyroxine is equivalent to 10 mg. of thyroxine.

also be noted that in the first patient the oral administration of 10 mg. of pure synthetic thyroxine in a single dose was without a clearly demonstrable effect on the basal metabolism. In the second and third patients, single doses of 10 and 7.5 mg., respectively, of synthetic thyroxine in the form of the monosodium salt produced increases in total excess calories only about one-third and two-fifths as great, respec-

tively, as the same doses by mouth in alkaline solution. In making these comparisons, only the results with synthetic thyroxine have been used.

In the first patient there was a normal amount of hydrochloric acid in the gastric contents after a test meal. In the second patient the amount of free and combined acid was small, both with and without histamine. The third patient showed no free acid and low total acidity before and after a test meal.

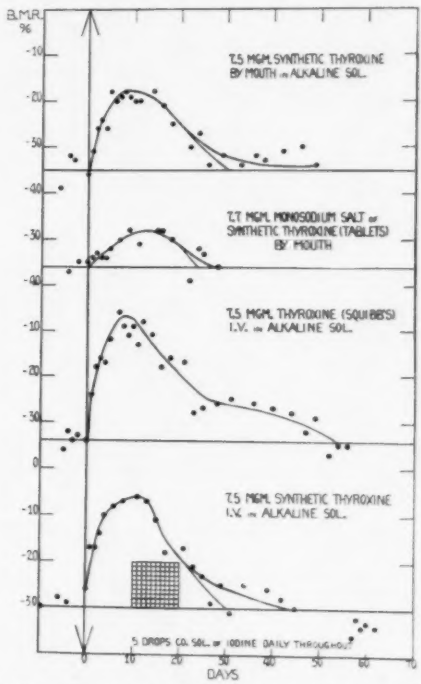
B.M.R. %
7.5 MGM. SYNTHETIC THYROXINE BY MOUTH IN ALKALINE SOL.
7.7 MGM. MONOSODIUM SALT OF SYNTHETIC THYROXINE (TABLETS) BY MOUTH
7.5 MGM. THYROXINE (SQUIBB'S) I.V. IN ALKALINE SOL.
7.5 MGM. SYNTHETIC THYROXINE I.V. IN ALKALINE SOL.
5 DROPS CO. SOL. OF IODINE DAILY THROUGHOUT
DAYS

Chart 6.—Detailed comparison of effects on basal metabolism of various administrations of 7.5 mg. of thyroxine in the third patient. The 7.7 mg. of monosodium thyroxine is equivalent to 7.5 mg. of thyroxine.

We believe that the extra alkali given as sodium bicarbonate probably had no effect on the final results because of effects recently obtained by administering 10 mg. of thyroxine by mouth in alkaline solution to three patients in the same manner as to the patients of this study, except that no sodium bicarbonate was given. In the first the basal metabolism rose from minus 34 to minus 10 per cent, in the second from minus 22 to minus 7 per cent, and in the third from minus 39 to minus 18 per cent.

Summary of Effects of Various Methods of Administration of Thyroxine on the Basal Metabolism and Excess Calory Production in Three Patients with Myxedema

Patient	Medication	Basal Metabolism Before Administration, % Normal	Level to Which Basal Metabolism Rose, % Normal	Surface Area Before Injection, Sq. M.	Number of Squares	Total Excess Calories	Excess Calories per Square Meter Body Surface	Per Cent of Rise in Basal Metabolism per Mg. Administered	Time Required for Basal Metabolism to Rise to Maximum, Days	Total Length of Time Basal Metabolism Affected, Days
1	10 mg. synthetic thyroxine intravenously in alkaline solution	—40	—11	1.52	1,150	14,860	9,775	2.9	9	80
	10 mg. synthetic thyroxine by mouth suspended in distilled water	—40	—35	1.52	24	310	205	0.5	1	8
	10 mg. synthetic thyroxine by mouth in alkaline solution	—40	—19	1.53	958	12,050	7,875	2.1	6	95
2	10 mg. synthetic thyroxine intravenously in alkaline solution	—26	— 1	1.42	408	5,135	3,615	2.5	2	29
	10 mg. natural thyroxine (Squibb's) intravenously in alkaline solution	—23	— 4	1.44	342	4,300	2,985	1.9	4	29
	10.3 mg. monosodium salt of synthetic thyroxine (tablets) by mouth	—25	—19	1.46	102	1,305	895	0.6	3	25
	10 mg. synthetic thyroxine by mouth in alkaline solution	—26	— 6	1.47	332	4,315	2,935	2.0	6	33
3	7.5 mg. synthetic thyroxine intravenously in alkaline solution	—30	— 7	1.63	476	6,910	4,240	3.1	6	45
	7.5 mg. natural thyroxine (Squibb's) intravenously in alkaline solution	—34	— 9	1.63	623	9,000	5,520	3.3	7	53
	7.7 mg. monosodium salt of synthetic thyroxine (tablets) by mouth	—36	—29	1.65	125	1,825	1,105	0.9	6	27
	7.5 mg. synthetic thyroxine by mouth in alkaline solution	—35	—19	1.65	342	4,990	3,025	2.1	5	42

COMPARISON OF EFFECTS OF SYNTHETIC AND "NATURAL" (SQUIBB'S) THYROXINE

Although the effects of synthetic thyroxine and thyroxine as isolated from the thyroid gland have been compared by several observers in different ways, few comparisons have been made in patients with myxedema, and about a year ago it became necessary for us to be doubly sure that these two substances were the same. Our data are recorded with those on the second and third patients. It may be seen that there are slight variations, which may be largely the result of slight variations in the levels of metabolism when the injections were given. The effect of synthetic thyroxine was slightly greater in the second patient and slightly less in the third, but the total change in basal metabolism and the total number of excess calories in each patient agree about as closely as might be expected in measurements of this sort. Similar curves have been reported by Møller, Gram and Schou.[7]

COMMENT

We[8] have just observed that in a patient with marked myxedema the basal metabolism which was minus 40 per cent before treatment could be maintained at the normal level by the prolonged daily oral administration of about 50 mg. of pure thyroxine suspended in distilled water. We have previously shown[9] that it is necessary to administer from 0.3 to 0.35 mg. of thyroxine intravenously every day to patients with marked myxedema to hold the basal metabolism at the normal level. Since the effect of thyroxine in alkaline solution by mouth is not less than one half of its effect intravenously, it would probably not be necessary to administer more than from 0.6 to 0.7 mg. in this form by mouth every day to hold the basal metabolism of a thyroidless person at the normal level. Although final figures have not yet been obtained for pure thyroxine, it would appear that, by the oral route, it is not more than one seventy-fifth as effective as its disodium salt, and that the monosodium salt is only about from one-third to two-fifths as effective. Pure thyroxine by mouth probably has not more than one-hundred-and-fiftieth as much effect as thyroxine given intravenously in alkaline solution. The reason for the slightly lesser

7. Møller, E.; Gram, C. N. J., and Schou, S. A.: Quantitative Clinical and Spectrophotometrical Comparison Between Natural and Synthetic Thyroxine, Acta med. Scandinav. **74**:85, 1930.

8. Thompson, W. O.; Taylor, S. G., III; Thompson, P. K., and Dickie, L. F. N.: Upublished data, 1933.

9. Thompson, W. O.; McLellan, L. L.; Thompson, P. K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: The Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, J. Clin. Investigation **12**:235, 1933.

effect of thyroxine in alkaline solution by the oral than by the intravenous route is not certain. A small amount may be destroyed in the gastro-intestinal tract or fail to be absorbed.

Our observations, together with those of Klein [2] and Baur and Loewe,[3] would seem to clear up much of the mystery about the supposed lack of absorption of thyroxine from the gastro-intestinal tract. Pure thyroxine is very insoluble in water and most organic solvents; the mono-alkali salts are slightly soluble in water, and the dialkali salts are easily soluble to the extent of about 4 per cent (Kendall [10]). When desiccated thyroid is given by mouth, digestion in the stomach and small intestine presumably results in the liberation of thyroxine in peptide combination and possibly of some free thyroxine. According to Harington and Salter,[11] thyroxine in peptide combination has a wide range of solubility. Salter, Lerman and Means [12] reported thyroxine polypeptide to be only slightly less active by mouth than thyroxine of the same iodine content given intravenously. We have recently noted that a peptide of thyroxine which Dr. S. Nadler prepared by the method of Harrington and Salter was insoluble in distilled water but soluble in an excess of sodium hydroxide. When administered by mouth suspended in distilled water our peptide produced about the same effect as the monosodium salt of thyroxine, whereas, when administered by mouth in alkaline solution, its effect was slightly greater than that of thyroxine in alkaline solution. The most important factor in the absorption of thyroxine from the gastro-intestinal tract would, therefore, appear to be the solubility of the compound administered. Salter, Lerman and Means [12] reported an increase in metabolism from about minus 37 per cent to about minus 8 per cent following the single oral administration of 13 mg. of thyroxine polypeptide containing 6.5 mg. of iodine, which is the amount contained in 10 mg. of thyroxine. They also reported increases from about minus 33 per cent to about minus 10 per cent and from about minus 37 per cent to about minus 10 per cent, respectively, in two patients following single oral doses of 10 mg. of thyroxine polypeptide containing 4.9 mg. of iodine. We have noted similar changes following the oral administration of our peptide in alkaline solution. In the six patients with myxedema in whom we have observed the effect of a single oral dose of thyroxine in

10. Kendall, E. C.: Thyroxine, New York, The Chemical Catalog Company, Inc., 1929.

11. Harington, C. R., and Salter, W. T.: The Isolation of l-Thyroxine from the Thyroid Gland by the Action of Proteolytic Enzymes, Biochem. J. **24**:456, 1930.

12. Salter, W. T.; Lerman, J., and Means, J. H.: The Calorigenic Action of Thyroxine Polypeptide, J. Clin. Investigation **12**:327, 1933.

alkaline solution, the increase in metabolism has been at the rate of from 15 to 24 points per 10 mg. of thyroxine. We feel that more data are necessary to prove conclusively whether or not thyroxine in alkaline solution has less effect by mouth than thyroxine polypeptide. We have just made observations which show that in different patients with myxedema a single large dose of desiccated thyroid may have either less or greater effect than a single oral dose of an alkaline solution of thyroxine of equal iodine content.

Our data clearly show that in preparing thyroxine for routine oral administration only the dialkali salt should be used. In this way it is possible to treat patients with myxedema almost as cheaply with thyroxine as with desiccated thyroid. We can now obtain tablets of the monosodium salt at a cost of 3 cents per 1.03 mg. Since the disodium salt is as easy to make as the monosodium salt, the cost should not be any greater. From the data presented it would seem that a patient with marked myxedema and a basal metabolism of minus 40 per cent would require not more than 0.65 mg. daily or about 238 mg. per year of disodium thyroxine to maintain the basal metabolism at the normal level. The yearly cost would be about $7. The same patient would require about 1½ or 2 grains (0.097 or 0.13 Gm.) daily of desiccated thyroid, containing 0.23 per cent of iodine. Such tablets may be purchased at the rate of 39 cents per hundred for the 1 grain tablets (0.065 Gm.) or 49 cents per hundred for the 2 grain tablets. Thus the cost per year for desiccated thyroid would be about $2. In brief, the disodium salt of the synthetic thyroxine, if used orally, would cost only about three and one-half times as much as desiccated thyroid. On the other hand, the comparatively enormous cost of using pure synthetic thyroxine by mouth may be noted. It would cost about $1 a day or $365 per year to maintain the basal metabolism of a thyroidless person at the normal level. If pure "natural" thyroxine were used, the cost would be about twelve and one-half times as great, or about $4,500 per year.

Since the form in which thyroxine is administered plays such an important rôle in its absorption from the gastro-intestinal tract, it is desirable that manufacturers should state precisely what their thyroxine tablets contain. Thus, one manufacturing company, on the labels on the bottles containing monosodium thyroxine, states that each tablet contains 1 mg. of crystalline synthetic thyroxine, whereas each tablet actually contains 1.03 mg. of the monosodium salt of synthetic thyroxine. When it is recalled that the pure substance has only about one thirty-fifth as much effect as its monosodium salt, the importance of making the distinction is obvious.

SUMMARY

In three patients with myxedema, single doses of 7.5 and 10 mg. of synthetic thyroxine in an alkaline solution had from 68 to 80 per cent as much effect on the basal metabolism when administered by mouth as when injected intravenously, in terms of the increase in basal metabolism and from about 72 to 84 per cent as much effect in terms of excess calory production.

The same doses given by mouth in the form of the monosodium salt to two patients had only from one-third to two-fifths as much effect as an alkaline solution given by mouth.

In one patient a single dose of 10 mg. of pure synthetic thyroxine by mouth produced too slight a change to be measured.

The solubility of any thyroxine compound administered appears to play an important rôle in its absorption from the gastro-intestinal tract and hence in its effect on the basal metabolism.

In two of the patients the intravenous injection of synthetic thyroxine produced approximately the same increase in basal metabolism as an equal dose of "natural" thyroxine.

Book Reviews

Handbuch der allgemeinen Hämatologie. Edited by Hans Hirschfeld, Berlin, and Anton Hittmair, Wels. Volume I. Price, 139 marks. Pp. 1,523, with 162 text figures, 43 colored plates and 4 plates in black. Berlin: Urban & Schwarzenberg, 1932-1933.

This handbook is so extensive that it will be impossible to discuss the details of any of its chapters within the limits allowed for a book review. A general survey of its contents is about all that can be attempted. Volume I has been completed, and the first half of volume II has also been published. The present discussion is concerned with the former, which is made up of a series of twenty-four monographs, five of which have been written by the editors and the remainder by other contributors, among whom there are many well known names.

As indicated by the title, this book deals with the general phases of hematology and not with the diseases of the blood as such. Many of the chapters, however, will be of great value to those whose interest is primarily in the diseases of the blood and their clinical aspects. Among these may be mentioned the sections on normal and pathologic morphology of erythrocytes (Günther), normal and pathologic physiology of erythrocytes (Denecke), normal and pathologic morphology of the leukocytes of the circulating blood (Hittmair), normal and pathologic physiology of leukocytes (Hirschfeld), blood metabolism (Bingold), blood volume (Seyderhelm), leukocytosis and leukopenia (Ernst Friedrich Müller), normal and pathologic morphology and physiology of the spleen (Wolff, Hirschfeld) and the effects of radiation on the blood and blood-forming organs (Halberstaedter and Simons).

Chemists will be interested in the extensive (pp. 99-222) and carefully written section on "Chemistry of Erythrocytes and of Hemoglobin" by Otto Schumm, Hamburg. This section contains about everything that could be included under the heading, and it is so well organized that it will appeal to readers who have only a general interest and whose chemical education may not be up to the demands of this difficult field. Among the topics considered are chemical composition of erythrocytes, hemoglobin and its relations to myochrome, myohematin and cytochrome, chemical structure of hemoglobin, globin, kathemoglobin and parahematin and hematin from plants. The different forms of porphyrin are treated in great detail.

The section on "Normal and Pathologic Morphology of Erythrocytes" by Hans Günther, Leipzig (pp. 1-98), begins with a statistical treatment of the number, volume and dimensions of erythrocytes under normal and pathologic conditions, including the effects of liver treatment on these values in pernicious anemia, and is followed by the mathematical calculations for volume and surface of erythrocytes. It is pointed out that the increase or decrease in the diameters of the red cells should be distinguished sharply from changes in volume. Thus in pernicious anemia the macrocytosis is largely an increase in average diameter (*Makroplanie*) without corresponding change in volume, while in hereditary hemolytic icterus the diminished diameter (*Mikroplanie*) is associated with an increase in volume up to 14 per cent. It is claimed that the elliptic form is the dominating one for all vertebrates, and that the degree of eccentricity shows differences that are characteristic of the species and individual. Hypereccentricity is constant in pernicious anemia but not in other conditions except the constitutional anomaly known as elliptocytosis. The remainder of the chapter is devoted to such morphologic features as Heinz bodies, basophilic stippling, Jolly's bodies and reticulation, contains a great deal of carefully analyzed information and is concluded with a discussion of endoglobular parasites.

In the chapter on "Normal and Pathologic Physiology of Erythrocytes" (pp. 223-269), G. Denecke discusses the origin, maturation and functions of these cells, together with the factors which influence their formation and delivery to the blood stream. The influence of the endocrine glands on the maturation of erythrocytes, the chemistry of respiration and the question of hemolysis as a factor in the final dissolution of the red cells are discussed in some detail.

In the section on "Normal and Pathologic Morphology of the Leukocytes of the Circulating Blood" (pp. 271-337), Anton Hittmair discusses general cell morphology, including atypical, youthful and aged forms, and the special morphology of the cells of the blood and of those that may appear in the blood in pathologic conditions. The section is illustrated with two colored plates and a large number of photomicrographs. The figures of the colored plates are mostly illustrations of different types of *Stammzellen* (stem cells) of which Hittmair recognizes a confusing number, some of which are not generally acknowledged by other hematologists. The chapter is altogether too brief, considering the territory covered, and references to the literature are often misleading. In the discussion of cell origins and relationships old terminology is often used with a new meaning which makes the chapter confusing to one who is not familiar with the literature of this field. The lymphoidocyte of Pappenheim (morphologically identical with Naegeli's myeloblast) is now a cell that shows reticulo-endothelial characteristics and is more primitive than the myeloblast. The hemocytoblast is also a more primitive cell than the cells described by Ferrata and Maximow under this same term. The blood cell-forming capacity of the undifferentiated mesenchyme of the adult is emphasized and illustrated, and it is pointed out that the undifferentiated mesenchymal cells and the different stages of their differentiation to various types of blood cells may appear in the blood in pathologic conditions. This leads the author to set up a series of histioid (reticulo-endothelial) stem cells which are inserted between the fixed stroma cell which has the capacity to form blood cells and the more highly differentiated myeloblasts, lymphoblasts and other cells. Ferrata's hemohistioblast (which Ringoen and Lambin believe is an artefact) is one of these intermediate cell types.

The "Chemistry of the Leukocytes" is discussed by Alfred Neumann, Vienna (pp. 339-380). He concludes that there is a distinct chemical difference between lymphocytes and granular leukocytes. Substances belonging to the Histon group are found only in the former, while glycogen is found only in the myeloid cells. Analogous leukocytes from different animal species show great chemical differences. Leukocyte granules are products of cell activity; they are colloidal and of complicated structure, as shown by Neumann's investigation of eosinophil granules, which were found to contain iron in variable quantity.

An interesting discussion of the physiology of leukocytes is found in the section by Hans Hirschfeld, Berlin (pp. 381-434). The following topics are considered: locomotion and motility, phagocytosis, bactericidal products from leukocytes, ferment action and metabolism. Only the leukocytes of the blood are considered, and physiologic problems other than those mentioned are left for other chapters.

The subject of "Blood and the Vegetative Nervous System" is considered in great detail by E. F. Müller, Hamburg (pp. 435-502). The discussion of the effects of nervous impulses on the distribution of the polymorphonuclear leukocytes (p. 483) is of special interest and importance.

A summary of the knowledge of blood platelets and hemokonia is given by A. Hittmair in the section dealing with these structures (pp. 501-548). The lack of figures makes the morphologic descriptions somewhat unsatisfactory. The following topics are considered: normal and pathologic morphology and physiology, embryology, origin and destruction of platelets, chemistry, counting methods, variations in number, the platelets in hemorrhagic diseases and the functions and properties of platelets.

The section on "Blood Formation in the Embryo" by William Knoll, Hamburg (pp. 553-600), is an exceedingly well written and illustrated (seven colored plates) chapter. Blood development at different embryonic periods in man and mammals

is considered in detail, and the knowledge of conditions in the lower vertebrates is summarized. It is pointed out that the primitive red cells of the first generation are identical with the megaloblasts of pernicious anemia, and that there are no transitions between these and the normoblasts of the second generation. The blood of an advanced case of pernicious anemia is much like that of the human embryo of the first month, including the large bell-shaped primitive erythrocytes. Some cases of icterus gravis neonatorum have a blood picture identical with that of the 3 or 4 month embryo. Facts like these show the practical value of studies on the blood in the embryo. Sixteen pages of bibliography complete this section.

K. Bingold, Nürnberg, has written an extremely stimulating section on *Blutstoffwechsel* (blood metabolism, pp. 601-646), based largely on his own researches. The experiments on the effects of living colonies of pneumococci on the hemoglobin of blood-agar mixtures heated to different temperatures are of special interest. The chapter attempts to answer such questions as, how does the organism dispose of blood from hematomas, which hemoglobin derivatives are encountered in the body, and can these substances be used as a measure of the rate of hemoglobin production and destruction, where does hemoglobin degradation end, and is iron metabolism an index of hemoglobin metabolism? The chapter is largely a discussion of the mechanism of hemoglobin synthesis and destruction and the changes which take place during respiration. It is one of the most lucid and interesting discussions of these topics that the reviewer has seen.

In the section on "Blood Volume" (pp. 647-734), Richard Seyderhelm (Frankfurt am Main) and Walter Lampe (Eschwege) present the details of various older and newer methods for determining blood volume, with a critical discussion of their value. They conclude that none of the methods give accurate results. The colorimetric method depending on the use of stains gives values for blood plasma only, while the carbon monoxide method determines only the mass of red corpuscles. Neither one of these methods gives correct values, but a combination of the two gives a figure for total blood volume that is sufficiently accurate to show significant changes in pathologic conditions. The influence of various physiologic (including the new-born and the infant) and pathologic states on blood volume is discussed, and there are tables to show values obtained by different methods.

The section on "Leukocytosis and Leukopenia" (pp. 735-868 and twenty-six pages of bibliography) by E. F. Müller is on a broad basis and contains much new material. General features are discussed at length, and the distinction between leukocytosis and leukopenia that are due to variations in distribution between peripheral and splanchnic vessels and the corresponding states resulting from hyperfunction or hypofunction of the marrow is emphasized. Leukocytes participate in the functions of different organs and tissues, and this is expressed by the increased retention of leukocytes in hyperactive organs. An attempt is made to correlate blood pictures with the state of the bone marrow, and the distinction between a hyperactive normal myelocytic and erythroblastic marrow and one that has undergone myeloblastic transformation is stressed. Clinical applications and diagnostic values are included in the discussion which represents a valuable contribution to this field.

F. J. Lang's (Innsbruck) section (pp. 895-941) is concerned with the mechanism of lymphocyte production in lymphatic tissues and organs and of myeloid cells in these same tissues in pathologic and experimental conditions. Myeloid metaplasia of the lymph nodes often begins as an intravascular process by the differentiation of circulating lymphocytes which have hypertrophied and become basophilic hemocytoblasts (identical with large lymphocytes). The germ centers of the follicles, besides producing and destroying lymphocytes, may also produce myelocytes by the proliferation and differentiation of the reticular syncytium and also by the differentiation of lymphocytes. The proof for these conclusions is presented in the form of five colored plates showing accurate drawings. Lang presents the subject from the extreme monophyletic standpoint and gives some of the best evidence available for the direct origin of myeloid cells from lymphocytes and undifferentiated connective tissue cells. He does not attempt to prove that this

occurs under normal conditions, or that the large lymphocyte or hemocytoblast is actually identical with the myeloblast.

The section on "Normal and Pathologic Morphology of the Spleen" (pp. 949-1031) has received adequate treatment by Erich K. Wolff, Berlin. Six pages are devoted to the development of the spleen and its hematopoietic function during the embryonic period. The normal histology, circulation of the blood and normal involution of the "white pulp" are considered at length. The pathology is treated as general pathology and as a series of selected topics among which are: the splenomegalies, the leukemias, the spleen in anemias, especially pernicious, and hereditary hemolytic jaundice.

Hans Hirschfeld, Berlin, gives a well organized critical review of the knowledge of the "Normal and Pathologic Physiology of the Spleen" (pp. 1033-1088). Besides the general physiology of the organ, topics like the following are considered: the spleen in infectious diseases and tumor immunity; its rôle in fat, lipoid, protein, carbohydrate and water metabolism; correlated functions of the spleen and other organs, and the splenic hormone. The author cites his own work to prove the influence of the spleen on erythropoiesis in the bone marrow, but concludes that the demonstration of this does not prove the existence of a specific splenic hormone. In the thirteen page bibliography the titles are arranged according to subjects.

The section on "Bone Marrow" by E. K. Wolff (pp. 1089-1130) is brief and leans heavily on the investigations of Maximow for the normal histology. Several of Maximow's excellent figures are reproduced. The origin and development of the different cell lines are considered, and the views of different authors are presented briefly. In the portion of the section dealing with the pathology of the marrow, general features are discussed, but there is considerable detail concerning the changes in the marrow in anemias, in polycythemia, in the leukemias and in tumors of the marrow. It gives a good survey of the principles involved in these changes in the marrow.

In the section on "The Reticulo-Endothelial System" (pp. 1131-1177), Günther Wallbach, Berlin, and E. K. Wolff present a useful critical survey and summary of the knowledge of this system, which can be recommended to all who wish rapid orientation in this difficult field. The subheadings give some idea of its scope: storage of colloidal dyes and iron, bile pigment formation and the reticulo-endothelial system, fat and lipoid storage, behavior in infections, immunity, blockade, functional tests, formation of blood cells and proliferative changes, including Gaucher's disease, Niemann-Pick disease, leukemic reticulo-endotheliosis and other conditions. The keen critical discussion of these topics is of special interest.

The section on "Results of Tissue-Culture Experiments with Blood and Blood-Forming Organs" (pp. 1079-1228) by William Bloom, Chicago, is a splendidly illustrated (eight colored plates and twenty-nine text figures) summary of what has been accomplished in this field. Clinical hematology has given abundant evidence for the derivation of lymphocytes, monocytes and myeloblasts from tissue cells (histiocytes), and tissue culture work has shown that the reverse process may also occur; i. e., histiocytes (polyblasts) and eventually fibroblasts may result from transformation of the cells named. Tissue culture has also contributed evidence (Maximow) for the differentiation of genuine lymphocytes to granular leukocytes, thus confirming the results of study of myeloid metaplasia described in the section by F. J. Lang. Those who have not followed the important literature in this field will find this an important chapter for rapid orientation.

The section on "Comparative Morphology of the Blood" by Dietrich Herzog, Giessen (pp. 1229-1318), gives an excellent summarizing, comparative study of the blood of all important groups of animals from sponges to vertebrates, and includes a reproduction of Gulliver's tables of measurements (calculated in microns rather than in fractions of an inch as in the original tables) of erythrocytes and leukocytes, and tables giving total leukocyte and erythrocyte counts and differential counts of various groups of vertebrates. The reader is not smothered with detail, but enough is given to show what may be expected in the different phyla and classes. The section would have been greatly improved by the addition of more figures to the

seven text figures which are presented. The literature, which is scattered through zoological, physiologic and anatomic journals and academy reports, is gathered together in an extensive bibliography.

The relationship between blood cells and the cells which participate in the process of inflammation is discussed by Martin Silberberg, Breslau (pp. 1319-1372). The nine colored plates give proof of the author's views, which coincide in the main with those of Maximow and are based in part on the study of material left by Maximow. The hypertrophy of emigrated hematogenous lymphocytes in the inflamed tissues, or of lymphocytes from cultures of blood to dye-storing histiocytes, and of the latter to fibroblasts, is well illustrated in the plates. The author has no sympathy for the view of von Möllendorff and others that the transformation may be in the reverse direction, i. e., that free histiocytes and lymphocytes may be derived from irritated fibroblasts. Although the discussion is brief, considering the amount of work done in this field, the author manages to refer to most of the modern literature in such a way that one can easily select the titles dealing with any phase of the problem.

I. Zadek, Berlin, has written the chapter on the "Cytology of Exudates and Transudates" (pp. 1373-1418). The five colored plates are probably the best figures that have been published on this subject. This section is especially welcome because hematologic texts give little or no information on this topic. The presentation is from the clinical standpoint and emphasizes the cytologic composition of the exudates of serous and joint cavities in various types of chronic and acute infections and in malignancy. A lengthy discussion is devoted to the exudates of chronic, acute, primary and secondary tuberculosis. Lymphocytosis and the lack of serosa endothelial cells are characteristic of the tuberculous exudate. Endothelial cells are abundant in hydrophilous and mechanical exudates and in malignancy of the bronchi and serous membranes. Genetic relations between serosa cells and lymphocytes are denied. Cells that seem to be intermediate between the two are interpreted as damaged or degenerating lymphocytes. It is the opinion of the reviewer that many of the phagocytic cells described and illustrated as endothelial cells are histiocytes which have originated from lymphocytes which have gradually transformed to the histiocytic type of cell. Such transformations can be seen in almost any experimental exudate from twenty-four to forty-eight hours after the intraperitoneal or intrapleural injection of aleuronat or some other irritant. (See also the section by Bloom.) Experimental exudates and questions of origin and genetic relationships which interest the hematologist receive scant consideration.

The volume is concluded with a clear and concise but comprehensive account of "The Effects of Radium, Kathode Rays, Roentgen Rays and Light Rays on the Blood-Forming Organs and the Blood" (pp. 1419-1520), by Ludwig Halberstaedter and Albert Simons, Berlin, which emphasizes the general effects of radiation and the biologic principles involved, but is not concerned with the details of therapeutic usage. Both the morphologic and the chemical changes resulting from irradiation are considered under the following major headings: changes in the blood-forming organs; effect on the structural elements of the blood; the hematopoietic organs and blood picture after the introduction of radio-active substances; effects on the blood plasma and its chemical constituents and on the coagulation of blood; influence on the sedimentation rate; damage to the blood and hematopoietic organs in professional radiologists.

In conclusion, it may be stated that the great size of the book (1,523 pages) is due to the large number of topics considered rather than to the exhaustive treatment of any one of them. The aim of the editors has evidently been to present a picture and summarizing account of the knowledge without giving an undue amount of detail and without the extensive discussions and speculations that one is accustomed to see in many handbooks. The specialist will wish for more discussion and more proof for many of the conclusions, but he who wishes only rapid orientation will be more than satisfied. The extensive bibliographies, sometimes arranged according to subjects, will facilitate further study.

HAL DOWNEY.

Practical Hematological Diagnosis. By O. H. Perry Pepper, M.D., and David Farley, M.D. Cloth. Price, $6. Pp. 562. Philadelphia: W. B. Saunders Company, 1933.

There has long been a demand for a practical clinical hematologic text in English. This book fills a definite need and contains sufficiently complete discussions of the various aspects of hematology to be of value to the general practitioner. It was not intended to be, and does not serve as, an encyclopedia of hematology.

The book is conveniently divided into three parts. The first part is devoted to the various components of the blood and methods of studying them; the second, to diagnosis of diseases primarily of the blood, and the third, to diseases not primarily of the blood. The laboratory findings in the various diseases are briefly and clearly stated, and the procedures that are most valuable in the differential diagnosis are discussed. The placing of references to key articles at the bottoms of the pages is of advantage. Theoretical discussion has been limited as much as possible, and the terminology has been limited to that used by the authors. A page devoted to a comparison of the terms used for the different cells would not have been amiss, and would have served as a distinct aid to the physician in reading other hematologic literature.

The hematologist will find certain faults. In the discussion of the leukemias there is lack of emphasis regarding the findings in the early stages, or in those cases which run their whole course with total leukocyte counts nearly or entirely within normal limits. Although in most cases of leukemia there is definite and marked leukocytosis when the diagnosis is definitely established, yet many of the patients have consulted their physicians because of symptoms related to the disease, and, because the leukocyte count was found to be nearly normal, the idea of leukemia has been discarded. The impression is obtained that in chronic myelocytic leukemia the leukocyte count is seldom nearly normal except in remission or following treatment for some intercurrent infection. One could hardly agree that the characteristic rise in the percentage of reticulocytes and the later rise in the number of erythrocytes and the percentage of hemoglobin are pathognomonic of addisonian anemia, since these features have been observed in other types of anemia.

The description of the morphologic details of blood does not reach the standard of the rest of the work. The authors' choice of a stain is Wright's modification of the Romanowsky stain. Some of the difficulties with this stain are mentioned, and it is stated that buffer solution, as recommended by McJunkin and Haden, may be used. It would have required only a few lines to give the formula for buffer solution which has solved the staining difficulties in many laboratories. Few of the people for whom this book was intended will have access to the references for this valuable adjunct to staining.

The description of some of the more immature cells is not consistent. Few hematologists would agree that "Its (the myeloblast) size and its nucleus are similar to those of the myelocyte." On page 144 is the statement, "it may be necessary to employ the oxydase stain to distinguish a myeloblastic from a lymphoblastic leukemia," whereas on page 150 is the warning that "the oxydase method cannot be trusted to differentiate the very immature cells of the myelocytic series from the lymphoblasts."

No mention is made of the pink-staining parachromatin as a feature of importance in identifying the normoblast. The differences between normoblast and megaloblast are not clearly defined. The discussion of the morphologic features of infectious mononucleosis is too brief to be of value in diagnosing a disease which constitutes one of the pitfalls of hematologic diagnosis. The changes in the neutrophilic granules in infections are held to be of little practical value, yet it has been shown by careful workers in this field that these changes may precede the nuclear changes in the same cells. The colored plates of the various blood cells are not well reproduced.

In spite of these criticisms, the book is a distinct addition to the library of the general practitioner who is interested in blood, since it serves as a ready reference to almost all phases of hematology and has been shorn of much of the unnecessary detail and discussion of theory and literature so often present in the hematologic textbooks in foreign languages.

Cancer du côlon droit. By Jean Gosset. Price, 50 francs. Pp. 328. Paris: Masson & Cie, 1933.

This work of Professor Gosset and his associates represents studies based on fifty patients with cancer of the colon. It is a comprehensive monograph of the subject, with a careful review of the anatomy—including an excellent consideration of the lymphatic drainage—and pathology. The photomicrographs of various specimens are clear and instructive. The author is still undecided as to the value and certainty of endeavoring to classify and establish a prognosis for cancers as suggested by Broders.

Although this is primarily an anatomicosurgical review, there is a rather brief, though excellent, résumé on symptomatology and diagnosis. The author deplores the late recognition of so many cases; in only twenty-six of his fifty cases was resection of the growth possible. The diagnostic value, with excellent illustrations, of the barium enema, combined with the technic of the injection of air, is included. He calls attention to the danger of barium administered orally in cases with obstructing lesions of the colon.

The different surgical procedures are discussed, and Gosset emphasizes the wisdom of a preliminary ileocolostomy and later resection. Ten patients underwent one-stage hemicolectomy, with one death, and sixteen underwent two-stage procedures, with two deaths; this is a splendid report. The gravity of any surgical procedure in inoperable cancer of the bowel is again illustrated, in that in this series there were eleven deaths among the remaining twenty-four patients.

This work may be summarized by stating that it represents an exhaustive review of the literature with discussions of all phases involved in cancer of the right side of the colon.

Trabajos de la Catedra de Semiologia. By Prof. T. Padilla. Pp. 664. Buenos Aires: La Semana Medica, E. Spinelli, 1933.

This is a collection of reprints from the department of symptomatology at the National Clinical Hospital in Buenos Aires. Naturally it is impossible to review them all. Most of the papers are on diseases of the heart. Cardiologists will doubtless be interested in the fourth paper, in which Dr. Padilla and his colleagues report their observations in three cases in which a catheter was passed through one of the veins of the arm into the right auricle, and in one case in which the right ventricle was punctured and blood removed. With this technic they were able to determine the minute circulatory volume. In two of the cases the values obtained with the indirect method were practically the same as those obtained with the direct method. In the others there was a difference of 20 per cent between the two figures. In another paper Padilla and Cossio describe the electrical disturbances that appeared when they punctured the right ventricle.

Other studies were made of the outlines of the auricles and ventricles as they project into the shadow of the barium-filled esophagus. Article eleven describes changes in the radiographic image of the heart during auricular fibrillation. In two papers Dr. Cossio describes the bronchial "dancing" up and down due to movements of the heart observed with roentgenocinematography. In this "dance" the bronchi, made visible with iodized poppy seed oil 40 per cent, descend suddenly and rise slowly. The movements are produced by expansion and contraction of the tip of the left auricle.

In article twenty-one there is a discussion of the hemodynamic action of the so-called cardiac hormones which are supposed to form in cases of myocardial insufficiency. Articles twenty-eight and thirty-three are on the treatment of hyperthyroidism with di-iodo-tyrosine.

Intracranial Tumors. By Percival Bailey, M.D., Professor of Surgery, University of Chicago. Price, $6. Pp. 475, with 155 illustrations. Springfield, Ill.: Charles C. Thomas, 1933.

This is an interesting book, well planned and well written. The material is divided into twenty chapters, beginning with an analysis of the problem of tumors in general and ending with the treatment of intracranial tumors, discussing on the way the anatomy of the brain, its physiology and the various manifestations of different tumors which develop in it. These are classified according to the author's views.

The charm of the book lies in the manner in which it is written. The author maintains throughout the volume a very individualistic point of view, describing cases to illustrate the subject under discussion as though he was giving a clinical lecture. Any reader, even if he is only cursorily interested in the subject of tumors of the brain, will gather a great deal of miscellaneous information about a field of medicine and surgery which of late has been intensively cultivated. He will do this pleasantly and easily. The more serious student of cerebral tumors will enjoy the orderly presentation of argument and will appreciate the bibliography of 421 references and the complete index of subject matter which end it.

As Dr. Bailey says in his preface, the method of illustrating the book may cause comment. The book is printed on dull paper and is illustrated with pen-and-ink drawings; roentgenograms are reproduced by diagrams or semischematically. Some readers will agree that this is an improvement in medical illustrating, while others will dislike it. In any event, Dr. Bailey would like to make the intricate subject of the localization and classification of tumors of the brain so interesting that all medical students will wish to understand it. His book is a fine effort toward attaining such a goal.

Acidosis and Alkalosis. By Stanley Graham, M.D., Visiting Physician, Royal Hospital for Sick Children, Glasgow, and Noah Morris, M.D., Biochemist, Royal Hospital for Sick Children, Glasgow. Price, $2.75. Pp. 203. New York, William Wood & Company, 1933.

This is a practical little treatise on acidosis and alkalosis, well written and therefore readable. It appears to have been published for medical students or for clinicians who might wish to brush up on so complex a subject as the reaction of the blood. Accordingly, it is simple in terminology and construction. Such matters as a definition of the terms which are employed, the carbon dioxide dissociation curve and the determination of the state of the acid-base equilibrium are competently handled. Clinical disorders such as diabetes, nephritis, cyclic vomiting and tetany are discussed from the point of view of their pathologic physiology. There is a practical chapter on the ketogenic diet with an appendix giving the ketogenic-antiketogenic values of foods, and methods of preparing molar and normal solutions. On the whole, the book is well worth while. It will prove useful for those for whom it has been written and should have a successful career.